Cancer pain:
interdisciplinary & comprehensive management

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Cancer Pain:
interdisciplinary & comprehensive management

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To Veronique
To Kristof and Filip

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List of abbreviations

CI	Confidence interval
CIVI	Continuous intravenous infusion
CSCI	Continuous subcutaneous infusion
IV	Intravenous
MS-CRS	Morphine sulphate controlled release suppositories
NSAID's	Non-steroidal anti-inflammatory drugs
PO	Per os
PCU	Palliative care unit
PST	Palliative support team
SC	Subcutaneous
SD	Standard deviation
TTS	Transdermal therapeutic system
VAS	Visual analogue scale
VNR	Visual numerical scale
VRS	Verbal rating scale
UH	University hospitals
WHO	World Health organization

Additional Theses

-Cancer patients not always like to be pain free.

- Caregivers, experienced as active listeners,
  are probably the best communicators for chronic patients

- Chronic benign diseases will frequently invalidate patients more than cancer, although they are less feared.

Chapter I:

General Introduction

General introduction

Dame Cicely Saunders founded the St Christopher's hospice in London in 1967. This was the first centre in the world dedicated to offer patients and their families effective palliative pain and symptom control. Knowledge and new attitudes towards optimal palliative medicine and care were gradually developed there and progressively spread over Europe and over the world in the following 30 years. The awareness of the need for skills in palliation increased, especially in the nineties. As a consequence an increasing number of all kinds of manifestations of interest in this field of medicine has appeared in books, journals and meetings and let to the creation of dedicated services for palliative care.

Palliative therapy and care are by definition the active, individually tailored, total care and the interdisciplinary management of the complaints and needs of the patients and their family, when the disease does not respond to curative treatment. In palliative care control of pain and other physical symptoms and of the associated psychological, social and spiritual problems is paramount. The primary goal is to try to achieve the best quality of life for patients and their families (1). Palliative patients must not be seen as medical failures for whom nothing more can be done. They need palliative care, which does not limit the care to just holding a patient's hand, but treatment demanding as much skill and commitment as is normally brought into preventing, investigating and curing illness (2). This does not imply that palliation only starts when all curative measures have been exhausted. Many cancer patients will benefit and will have a better quality of life during their treatment if the principles of pain and symptom control of palliative care would be implemented much earlier in the course of the disease than at the turning point from cure to care.

1.1 Comprehensive symptom control during the course of the illness

Good symptom control ensures a better quality of life for the patient during the course of any disease. This is especially true for cancer patients due to the wide variety of symptoms that can exist at the same time or consecutively in these patients. Cancer is a multi-symptomatic disease and pain is not the only factor that can disturb a patient's quality of life. Symptoms are caused directly or indirectly by the illness, but in addition the side effects of the treatment (surgery, radiation therapy and systemic therapy) can also cause significant discomfort. Among the different symptoms, pain is not only the most feared by the patients, but also one of the most frequent symptoms (46-71%). Next to pain, fatigue (43-82%) is the most frequent symptom; the other relative frequent symptoms in cancer patients are weight loss, anorexia, constipation, nausea/vomiting and depression; they are less frequent ($\pm$20%) than pain and fatigue in the different studies (3). The same attention that is required to control pain must be directed towards managing other symptoms and discomforts in order to provide cancer patients an optimal quality of life at all stages of the disease (4). Palliative care principles and cancer pain management should be considered as part of a comprehensive cancer management (5). Pain occurs in about 50% of all patients treated for cancer. Pain relief measures and anti-cancer treatment have to go hand in hand. More than two thirds of patients with advanced disease experience pain; therefore the management of pain and other symptoms becomes the main aim of treatment in many cases (6). Of all symptoms occurring in advanced disease, pain is probably the most amenable to treatment. Yet, even in developed countries, over half of these patients do not receive an adequate level of analgesia, while experience in optimal palliative settings has proven that approximately 90-95% of these patients can be treated for their cancer pain if knowledge already available is used (7).

This unacceptable situation still exists because there is limited understanding of the nature of cancer pain in clinical oncological practice. There also is a failure to fully appreciate that pain is not only a physical sensation, but that psychological, social and spiritual factors contribute to pain experience. There still is a belief amongst many patients and caregivers that pain in cancer is inevitable and untreatable. Finally there also is reluctance to apply the well-established principles of the management of cancer pain, arising from inadequate education and confounded by irrational fears concerning the use of opioids (7).

The suboptimal treatment of cancer pain has many causes, the most important of which probably is inadequate assessment (8). The discrepancy between the patient's and the physician's evaluation of the severity of the pain problem is a major predictor of inadequate pain relief (9). But some clinicians remain unwilling to prescribe sufficient doses of opioid pain relievers in part because they do not distinguish either morally or psychologically between actions performed with the intent to cause death and actions performed with the possibility of an adverse event resulting in death (10). US-clinicians to some extent are discouraged from prescribing or administering adequate doses of drugs to relieve symptoms of dying patients by the Pain Relief Promotion Act of 1999. This bill states that physicians may use controlled substances to alleviate pain or discomfort, even if the use of such substances may increase the risk of death. But the same bill forbids 'intentionally dispensing, distributing or administering' a controlled substance for the purpose of causing death (11). Patients as well as doctors often have exaggerated fears of addiction and the side effects of narcotics. The second part of the bill still causes suboptimal treatment of patients who need very high doses of opioids at the end of life because physicians fear to be prosecuted.

1.2 Cancer pain can and must be treated

For many people, a diagnosis of cancer equals the expectation of a painful and debilitating illness, culminating in a distressing and perhaps meaningless death. The

process of dying, and in particular concern regarding uncontrolled pain, is often feared more than death itself. Prompt and effective relief of pain is a fundamental principle of palliative care that is enshrined in its very definition. The International Association for the Study of Pain already exists more than 20 years and we now have better understanding of pain and of the pharmacology of analgesics (12). The World Health Organization published a clinical alert three times since 1985 to optimize the relief of cancer pain (1, 5, and 13). The European Association of Palliative Care was founded in 1989 to collect all available knowledge and to provide guidelines to optimize palliative care, with a focus on cancer pain management and research in palliation (14). The American Pain Society reported in 1992 that relief of pain in cancer patients is an ethical imperative and it is incumbent upon clinicians to maximize the knowledge, skill and diligence needed to perform this duty (15).

The aim of treatment is to relieve the pain to the patient's satisfaction, so that he or she can function effectively and eventually die free of pain. This implies that treatment has to be tailored to the individual, with drug treatment and anaesthetic, neurosurgical, psychological and behavioural approaches tailored to the individual patient's need.

1.3 Epidemiological data

The number of cancer patients in the world is increasing, mainly because of the aging population and the increase in tobacco consumption (6). At least 50-70% of all cancer patients will suffer pain some time during their disease. In a large German study of terminally ill cancer patients only 9% of the patients required no systemic analgesics. Non opioid analgesics were effective in 5% and a combination of non-opioids and "weak" opioids in 16 % of the patients. In the remaining 70%, "strong" opioids alone or in combination with non-opioid analgesics were necessary to achieve adequate pain control. Additional co-analgesics and adjuvant drugs to treat special types of pain or other symptoms were prescribed in 90% of the patients

(16). In an updated German 10-year prospective study, 2118 patients were assessed over 140.478 treatment days (mean of 66 days/patient) during cancer pain relief and palliative care programs. Non-opioid analgesics (WHO step I) were used in 11%, weak opioids (WHO step II) in 31% and strong opioids (WHO step III) in 49% of treatment days. Analgesics were administered via enteral route on 82% and parenteral on 9% of treatment days. In the remaining days, either spinally applied opioids (2%) or other treatments (6%) were utilized. Fifty-six percent of the patients were treated with morphine. Over the whole treatment period, good pain relief was reported in 76%, satisfactory efficacy in 12% and inadequate control in 12% of the patients. Other frequent symptoms were neuropsychiatric disorders on 23% of days, nausea (23%), constipation (23%) and anorexia (20%) (17). In another study cancer pain also was the most frequent symptom in 67 of 126 patients (53%) receiving home care, and it could be effectively controlled with morphine; no patient returned to the hospital because of aggravation of pain (18). In the palliative care unit of the University Hospital of Leuven, 80% of the first 250 patients that died there used strong opioids for pain relief during their terminal phase of life.

1.4 The concept of "Total Pain"

The International Association for the Study of Pain provides the following definition: "Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life. It is unquestionably a sensation in a part or parts of the body but it is also always unpleasant and therefore an emotional experience" (12). The above definition has two major strengths: firstly clinicians have to begin to learn to believe patients when they complain of pain and secondly, the definition recognizes the importance of the emotional factors in the appreciation of pain. In fact the pain perception threshold may be relatively constant for all individuals; the pain tolerance threshold is subject to considerable variation and

may be influenced by physical, emotional, social and spiritual factors (19). Sometimes is the threshold for physical pain so much influenced by existential concerns, social or spiritual components, that these factors become overwhelming in the total pain experience and that we probably better change the word 'pain' to existential, social or spiritual 'suffering' .

For the clinician it is important to take the patient's complaint of pain serious. Characteristics of the pain have to be defined by site, by onset, by quality and by intensity. This last aspect is mostly quantified with the visual analogue pain scale. Behavioural treatment methods have not been as widely implemented as pharmacological treatment methods in cancer pain. This is in contrast to treatment of non-malignant chronic pain where cognitive and behavioural programs are commonly applied (20). Cancer pain in most cases has a nociceptive basis. It however still is a multidimensional process, and thus potentially modifiable by non-pharmacological factors. For this reason, pain management is an interdisciplinary activity and it's no longer possible for one physician to competently cover all the different aspects of life that can influence pain perception.

1.5 Acute and chronic pain

The association of particular pain characteristics and physical signs with specific consequences of the underlying disease or its treatment defines pain syndromes. The evaluation of pain characteristics provides some of the essential data for syndrome identification. These pain characteristics are intensity, quality, distribution and temporal relationship. Knowledge of the pathophysiological processes can help to distinguish between nociceptive and neuropathic pain and is directly important for the management of pain. Idiopathic pain, with no identifiable organic pathology or related to a psychiatric disorder, is uncommon in cancer populations.

Cancer pain is a chronic pain and has to be distinguished from acute pain in many aspects. Acute pain occurs in response to tissue injury or damage and the expectation is that, as healing occurs, the pain will lessen. The pain may even serve a useful function by forcing the patient to spare the damaged part, thereby enhancing the process of healing. Chronic pain occurs in a situation where it is unlikely that further healing will occur. In fact, because cancer is a dynamic process, more tissue damage is probable. The chronic pain as a consequence of advancing cancer serves no useful purpose. It is no longer a symptom of tissue injury or damage, but a hurting syndrome on its own. In advanced cancer, the symptoms are the disease (21).

For all these reasons it is justified but also a challenge to treat cancer pain with proper assertivity and aggressivity. The goal of treating chronic cancer pain is not simply pain relief but also pain prevention. For sustained analgesia in most cases, around-the-clock dosing has to be instituted. Pain treatment on an “as needed basis” is inappropriate in most cases for two reasons. First of all, cancer patients are confronted with “chronic” pain that gradually will increase when the disease becomes more advanced. So the pain will return after a single administration of analgesics and there is no reason to let the patient suffer again before the next dose of analgesics is given. Secondly, the patient will try to postpone the intake of the following drug dose because in general he prefers to suffer some pain instead of taking analgesics on a regular and continuous basis. One of the challenges is to eradicate this misconception from the minds of patients, of families and especially of caregivers. Supplemental rescue doses of analgesic drugs should be available to all patients for breakthrough and incidental pain due to progressive disease, activity or stress. As a guiding principle, the total maintenance dose plus the as-needed rescue medication in a specific time interval should become the regular dose during the next identical time period. The dose of the breakthrough pain medication is 1/12 to 1/6 of the daily maintenance dose for pain intensities respectively below or above VAS-score 5 (14).

Pain prevention also is an appropriate goal in the management of acute moderate-to-severe pain that is expected to last more than 24 hours. Resolution of the source of the acute pain should be anticipated with regular downward dose titration if the pain is well controlled without the need of additional analgesics. Therapy of acute pain that is not expected to last more than 24 hours can consist solely of treatment on an as-needed basis (22).

1.6 Cancer pain can be multi-factorial and multi-focal

Pain in cancer patients can be classified in four different groups (23):
-Pain caused by the cancer itself; this is the most frequent reason (61%). The tumor can invade bones, soft and visceral tissues and peripheral nerves.
-Pain caused by the treatment, like surgery, chemo- or radiotherapy. This pain can be more acute during or shortly after the therapy, or the pain can be chronic as a late effect of the treatment (5%)
-Pain caused by general weakness, aches and stiffness associated with prolonged immobility and weakness (12%)
-Finally there is pain that is unrelated to the cancer or its treatment; patients can also have other than cancer related pain due to degenerative, ischemic or inflammatory pathology (22%).

In many patients, cancer pain can present at different sites at the same time. In one study, 4 or more separate sites were painful in 34% of the patients. This is of practical importance since the underlying cause of each of these pains may well be different, and consequently each may require a separate line of management (24).

1.7 Palliative oncological treatments

Surgery, radiotherapy, chemo- and hormonal therapy are very effective palliative treatments for pain and symptom control, in combination with analgesics as needed, as long as the anti-cancer treatment is effective.

Surgery is the most effective pain treatment option when a pathological fracture can be stabilized. Other good palliative surgical results are obtained by pleurodesis or by placement of derivative stomas on the colon and ureters or with small bowel bypass surgery.

Radiotherapy is a very effective treatment for painful bone metastases, to resolve obstructions caused by tumor compression of blood or lymphatic vessels, of airways or the gastro-intestinal tract. Ulcerating tumors and hemorrhage in tumoral tissue can very effectively be irradiated to comfort the patient. Also neuropathic pain by nerve or plexus invasion or headache by intracranial hypertension secondary to brain metastases are frequently very good indications for palliative radiotherapy.

Except in the case of lymphomas and small-cell lung cancers, chemotherapy is not a fast effective palliative treatment. However, in less urgent situations, chemo- and hormonal therapy can result in very long-lasting relief of pain and other symptoms, sometimes even for years, as is frequently seen in metastatic breast and prostate cancer. But there comes a time in the advanced cancer patient that anti-tumor treatment no longer remains a valid option, while before this turning point it frequently was the first choice of treatment for pain and symptom control.

After that turning point, drug treatment becomes the mainstay of cancer pain management. But if we focus all our efforts on achieving control of pain, without regard to all other factors like anxiety and depression, it is highly unlikely that we will achieve an optimal level of success (25). The effective treatment of chronic pain needs a multidisciplinary approach. It is not just the application of the necessary skills involved; success also requires a relationship, based on trust, between the patient and the professional caregivers so that emotional and psychological aspects also can be considered (26).

1.8 Pain assessment and measurements

A physical examination, including a neurological examination, is a necessary part of the initial pain assessment. The physical examination should attempt to identify the underlying causes of the pain problem, clarify the extent of the underlying disease and discern the relation of the pain complaint to the disease. Expert assistance from physicians in other disciplines, nurses, social workers, or others may also be necessary to evaluate related physical or psychosocial problems identified during the initial assessment. Pain must be managed during that process to improve compliance and reduce the distress associated with procedures. No patient should be inadequately evaluated because of poorly controlled pain (27). Careful review of the laboratory and imaging studies can provide important information about the cause of the pain and the extent of the underlying disease. Additional investigations are often needed to clarify uncertainties if appropriate to the patient's general status and the overall goals of care (27). In a comprehensive pain assessment in the management of patients with cancer, a pain consultant at Memorial-Sloan-Kettering Cancer Center identified a previously undiagnosed etiology for the pain in 64% of 276 consecutive consultations. The most common diagnosis was metastatic tumor and new neurological diagnoses were established in 36% of the patients (28). Besides a careful history and clinical examination there was a need for 264 radiographic and 16 laboratory studies, 6 lumbar punctures and 1 electromyography.

It is essential to establish the cause or the causes of the pain before planning pain treatment. A detailed pain assessment as just mentioned will gather the necessary information to make the correct clinical diagnosis. This diagnosis has to be explained to both the patient and the family. They have to understand what the aims of the treatment are and what they can expect or not expect.

Regular evaluation of both the therapeutic effect on pain and the intensity of the side effects are mandatory for all patients who suffer from chronic pain. To evaluate the result of pain treatment, there is a need for a reliable and accurate way of pain measurement. The greatest single problem may be inadequate pain assessment by the patient and the caregivers. Informing caregivers and patients that their cooperation in pain treatment is essential can rectify this deficiency.

The tool used most frequently is the numerical rating scale (NRS); it is a one-dimensional scale (29) that consists of a horizontal or vertical line evenly anchored or divided into 10 segments numbered consecutively between 0 and 10. Patients may be instructed that 0 represents “total absence of pain” and 10 denotes the “most severe pain they can imagine”. The patient is instructed to simply mark the number that best describes the level of pain he is experiencing at a given point in time.

Technically, for such a scale to be truly visual analogue in character (visual analogue scale or VAS), it should consist of only a line with anchors at both ends and none in-between. This is the simplest tool of pain measurement that just quantifies the pain intensity, but lacks some qualitative information about the pain (29).

A modified visual-scoring system for use with children substitutes a continuum of smiling to crying faces for numbers (30). A verbal rating scale (VRS) with indications “no, mild, moderate, severe, intolerable” proves easier to apply and may be more reliable in the presence of cognitive impairment (31).

A more comprehensive scoring system is the Mc. Gill Pain Questionnaire (MPQ) (32) that is widely recognized as a valid and reliable instrument to measure pain. It’s a pen and paper instrument that, in addition to other components, instructs the patients to make relevant selections from a list of 78 adjectives used to describe pain. The selected adjectives help to evaluate the extent to which pain is predominantly sensory or affective (33). Another feature of the MPQ is a schematic representation of the body that is shaded by the patient to indicate where pain is located. This component can be modified to provide additional information by instructing the patients to inscribe a numeric value that signifies regional pain

intensity in the shading areas. The MPQ is also relevant to assess the patient's psychological status, although there exist other sophisticated questionnaires (Wisconsin Brief Pain Questionnaire measures pain and does a careful psychometric analysis, the Varni Thompson pediatric brain questionnaire has been formulated in separate versions for children, adolescents and parents) to assess psychological factors that often have an important bearing on pain, such as the patient's personality, the presence of depression or anxiety, hypochondria, preoccupation with body image, etc.(34). While a comprehensive battery of psychological testing is usually considered to be an appropriate component of the assessment of the patient with chronic non-malignant pain, it is essential that testing of the cancer pain patient be brief and not excessively demanding. Several practical and useful tools have been introduced that specifically target patients with cancer pain and that possess these attributes. These include the Wisconsin Brief Pain Inventory and the Memorial Brief Pain Assessment Card (35). The latter is a simple, efficient and valid assessment instrument that can provide rapid evaluation, in clinical settings, of the major aspects of pain experienced by cancer patients. It consists of a two-sided card with 4 scales to measure the intensity of pain, the pain relief, mood and a set of descriptive adjectives.

Patients have to be taught how to use pain measurement tools and how to rate and to register their pain scores. This has to be discussed daily at the start of the pain therapy and, when the analgesic dose is stabilized with good pain relief, a weekly discussion between patient and physician seems sufficient (36).

1.9 Analgesic drugs

When anti-tumor treatment no longer is possible, symptomatic pain relief becomes the mainstay of treatment. The analgesic drugs are chosen according the WHO analgesic ladder for cancer pain management (6).

The sequential use of the drugs according to the WHO ladder allows prescription adapted according to respectively mild (VAS-score 1-3), moderate (VAS-score 4-6)

and severe (VAS-score 7-10) pain. Only one drug belonging to steps II and III should be used at the same time; adjuvant drugs should be given for specific indications. The non-opioids of step I (paracetamol, salicylates and the non-steroidal anti-inflammatory drugs) are used for mild pain. These three different non-narcotic analgesics can be used separately for mild pain or the NSAID's can be combined with paracetamol or salicylates to be more effective.

Patients with moderate pain should be treated with weak opioids (WHO step II), where codeine is the reference drug. A combination with two or more analgesics belonging to step II (tramadol, paracetamol-codeine, tilidine, propoxifene and buprenorphine) is never indicated. When a step II drug ceases to be effective at its maximum dose, it is recommended not to switch to another drug of similar efficacy but to prescribe a drug that is definitely stronger (step III).

Morphine is the reference drug in step III but also fentanyl and methadone belong to step III. The analgesic drugs of step II have to be stopped and are replaced by strong opioids, starting with the appropriate dose of long-acting equivalent of 60mg oral morphine per 24h. Breakthrough medication with short acting morphine needs to be available for all patients treated with strong opioids. Sometimes a step I analgesic drug is added to the therapy with weak or strong opioids to obtain a more potent analgesic effect. A typical indication is the combination with paracetamol or NSAID's for bone pain or pain to which some inflammation contributes. Major indications for ketorolac are pain associated with trauma to bones and muscles, but also cancer related pain, in which a "saving effect" on simultaneously employed opioids can be achieved (37). Due to its long half-life, methadone is not a preferred painkiller in cancer; it can be difficult to adequately adapt the dose while the pain score is increasing. Secondly there is a risk of delayed toxicity as plasma levels of methadone gradually rise due to dose increments or a major organ failure which frequently happens in terminal patients.

Fentanyl is applicable as a transdermal therapeutic system (TTS-fentanyl) that is as effective as morphine but has a more favorable profile of side effects, especially at very high doses, for patients of all ages.

All the analgesics of step I and II, except buprenorphine, have a ceiling effect. This implies that no better analgesia is obtained by increasing the dose above the advised maximum dose, only the side effects increase. Morphine, methadone and fentanyl however, do not have such a ceiling effect. There is a linear relationship between the plasma concentration of morphine and increasing doses. An analgesic effect is obtained with higher doses for pain not controlled with the lower doses.

The fear of physicians, nurses, patients and family to induce addiction or tolerance by using strong opioids is partly responsible for the insufficient use of opioid drugs. But available studies indicate that in cancer patients iatrogenic addiction is quite rare (less than 1%) and the risk of a major tolerance is very small (38). In general, families are more anxious about morphine than the patients themselves. In a study of 539 patients one addicted patient (0, 18%) was found, who however had begun drug use long before pain treatment was required (39).

The use of lower doses of morphine is possible when concomitant non-opioids and specific co-analgesics are used. The lower doses result in a lower incidence of side effects; in a long-term survey, constipation and nausea/vomiting were the most common side effects of morphine while tolerance and addiction did not appear (40). The co-analgesics can potentiate the morphine analgesia by causing an increased bioavailability of the opioids, but also by an intrinsic analgesic effect. Corticosteroids have an anti-inflammatory action and decrease edema, so they can decrease pain due to intracranial hypertension or decrease the tension on the liver capsule in an enlarged metastatic liver. The use of an antidepressant or anticonvulsant is suitable when a neurogenic pain component is present. The use of antidepressants is indicated when a deafferentiation pain is present or when there is a concomitant depressive illness (41).

1.10 Analgesic drug administration in cancer pain

1.10.1 Oral administration

Both the World Health Organization and the European Association for Palliative Care advise to administer the analgesics orally for chronic cancer pain (1, 14). This is an inexpensive and yet effective method for relieving cancer pain in more than 70% of the patients. In this way the patients are independent from their caregivers. A double dummy, crossover study on 52 cancer patients compared controlled release morphine suspension and controlled release morphine tablets. There was no statistically significant difference in severity of pain assessed on a visual analogue scale, the need for rescue doses of immediate-release morphine, treatment preference by the patients, and indices of quality of life (activity, mood, and sleep). This study showed that, when prescribed in the same doses, controlled release suspension and tablets have similar efficacy and adverse effects, as well as the same duration of action (42). Although oral administration of analgesics is standard clinical practice, a significant proportion of patients cannot be treated in this way. It has been estimated that more than 50% of patients with advanced cancer will eventually be unable to tolerate oral morphine (43) because of problems with swallowing, persistent nausea and vomiting, bowel obstruction, intolerance to oral opioids, incident pain or poor compliance to an oral regimen (44).

In a study of 100 patients, the majority required at least 2 administration routes and 1/3 of the patients required 3 routes of administration (45). The oral route is usually preferred, because it is simpler, easier to use, and less expensive than parenteral therapy (46, 47). There is limited bioavailability of some opioids, the alterations in metabolism that are associated with presystemic elimination (liver first pass effect), the slightly slower onset of analgesia and the delayed peak time all support the need for other routes of administration that may avoid these disadvantages. Subcutaneous or intravenous administration of morphine or hydromorphone is preferable to

transdermal administration of fentanyl in patients who are unable to take oral medication for 24 or 48 hours or for a longer time because of severe nausea, vomiting or gastro-intestinal disorders. Also for patients with frequent episodes of incident pain or patients with acute, severe pain who require rapid onset of analgesia, SC or IV injections or infusions are preferred over the other administration routes (22, 48).

1.10.2 Transdermal administration

Once equilibrium is reached, the transdermal fentanyl system maintains serum concentrations of fentanyl similar to those found with constant intravenous infusion. The analgesic effect of transdermal fentanyl is proven. There are a number of potential benefits to this administration route. The system is more convenient for the patient and the caregivers than the parenteral, rectal or spinal routes, and the overall costs are much lower (49). It can be used in patients who are unable to tolerate oral morphine, and are too sick or confused to be taught how to use a patient-controlled infusion pump. When compared with the oral administration, it is also potentially advantageous, largely due to the 3-day dosing. This reduces staff time in administering the drug and may also improve patient compliance. It may be suitable for patients who can tolerate oral opioids, and appears to be a highly beneficial alternative for those who cannot (50). The patient is more independent from the caregiver and there no longer is a reason for clock watching. Possible disadvantages of transdermal administration include a long latency of onset after application and the continued absorption from a subcutaneous depot after the patch is removed, resulting in a slow decline in plasma concentration after removal. During the dose titration and stabilization period, patients may require other opioid analgesics, and these may also be required for breakthrough pain once patients are stabilized. The transdermal application system is most suited for patients who have relatively stable levels of pain. Significant increases in TTS-fentanyl (Transdermal Therapeutic System) were necessary during weeks 1 through 4 to maintain pain

control. Fifty-nine percent of the patients needed one or more dose increases (50). Patients and physicians reported satisfaction with the transdermal fentanyl therapy, 95% of the patients prefer to continue the transdermal fentanyl therapy at the end of the study, due to better performance in comparison to oral morphine (51).
Transdermal fentanyl probably is not a good analgesic drug for patients with generalized edema, for those who are medically unstable, who need analgesic drug titration, who need frequent dose changing, or when frequent breakthrough pain is present.

1.10.3 Parenteral administration

Subcutaneous, intramuscular or intravenous injections of morphine at regular intervals can control moderate and severe cancer pain in most patients (52) and is common practice when oral medication cannot be taken. However injections need to be repeated every 4 hours. This is undesirable because it becomes painful for the patient, time consuming for the nursing staff, and difficult to maintain in the home setting. The injections are often “complicated” by the occurrence of a prominent “bolus” effect. Some patients experience marked toxicity at high peak plasma levels, with nausea, vomiting or somnolence, while injections offer no pharmacokinetic advantage. For all these reasons regular injections are not recommended (53).
Repeated bolus doses can be accomplished without frequent skin punctures through the use of an indwelling subcutaneous (S.C.) infusion device. The appropriate selection of the right opioid drug and a continuous route of administration were associated with improvement in pain relief and a lower prevalence of cognitive impairment, hallucinations, nausea, vomiting and myoclonus among patients who were discharged from the hospital (54). Already since 15 years studies have proven that continuous intravenous infusions (C.I.V.I.) of analgesics are safe and effective to treat both postoperative and cancer pain (55). Continuous subcutaneous infusion (C.S.C.I.) was already in 1988 experienced as effective and comfortable that after

48 h. use even 94% of 108 patients preferred the subcutaneous infusion to the continuous intravenous or repeated intramuscular route. Forty-seven percent (n = 33) of the patients (n = 70/108) treated with a portable pump were discharged home (56).

Ventafridda treated in the same era 40 patients with a syringe driver with pain relief as good as intermittent injections, while less nausea was seen with continuous S.C. infusion (57).

The Pharmacia-5800 pump allowed the patient to give himself a bolus during the continuous infusion and this improved pain control in all patients (n = 18) in the study of Kerr; 5/18 patients could die at home with the support of their family (58)

In the first years of the use of C.S.C.I., there was some concern about the possible irregular absorption of the subcutaneously injected analgesics. Waldmann et al. measured blood levels of morphine in 9 patients receiving C.S.C.I. and in 4 patients receiving C.I.V.I. They found no difference between C.I.V.I. and C.S.C.I. (59). Peak plasma levels are achieved within 15-20 minutes of intramuscular and subcutaneous and within 30-90 minutes after oral administration. Peak levels after oral administration are much lower than after parenteral administration, since oral morphine undergoes extensive first-pass metabolism in the liver (59).

After starting C.S.C.I. of strong opioids, the site of infusion has to be checked daily and the infusion place should not be changed until signs or symptoms of local intolerance develop (pain, redness, swelling, leakage). The mean duration of infusion at a single site was 7.3$\pm$5.2 days (range 1-29) for 119 sites in 45 patients (60). The most frequent signs of local toxicity were redness and swelling without serious local complications; these results suggest a weekly change of infusion site to be appropriate.

Morphine is the drug of choice when parenteral strong opioids are necessary to relieve severe cancer pain. When unacceptable side effects occur, morphine can be replaced by a continuous subcutaneous fentanyl or sufentanil infusion. Both can achieve good analgesia with a low rate of adverse side effects (60). Patients, who

cannot swallow, with severe nausea or vomiting, with malabsorption, are candidates for this treatment modality. Patients who need extremely high doses and who have some discomfort swallowing pills, or who have decreased consciousness due to the high dose, can also switch to C.S.C.I. Patients who experience adverse effects from the peak serum levels when opioids are given intermittently can benefit from a continuous infusion. Renal failure is one of the rare contra-indications for C.S.C.I. because of the risk of accumulation of morphine that will result in excessive sedation and confusion for several hours or even days. Therefore, in addition to breakthrough pain, the presence of renal failure is the only other reason to give analgesics as needed. The programmable computerized infusion pump was found to be more cost-effective than the disposable infusion device after a break-even point at 8 months (61).

Because of the simplicity, technical advantages, and cost effectiveness of continuous subcutaneous opioid infusion into the chest wall or the trunk, intravenous opioid infusion for the management of severe cancer pain should be abandoned. Drugs given by the subcutaneous route have a reliable absorption and this method has been demonstrated to be safe and effective in cancer pain management. On this basis, it should be considered the standard alternative route against which all newer routes of administration should be tested (62).

Many oncological patients previously had chemotherapy via implanted central venous catheters systems. These venous access devices can be used to administer drugs for symptom control like analgesics, anti-emetics or sedatives. However parenteral administration can also cause some discomfort to patients, in some cases it can result in sepsis (IV) or tissue irritation (SC). Although cancer pain management is mainly managed intravenously in hospitals, there are little scientific data available in recent literature concerning this administration mode. Due to the growing use of venous access devices to administer cytostatics, patient controlled analgesia with a portable pump linked to these devices has becomes feasible and allows patients to return home without changing the administration route. One of

the advantages of the intravenous route is the greater possibility of mixing different drugs while there are sometimes limits to the volume of these mixtures that can be given in a continuous subcutaneous infusion. A continuous drip infusion of morphine progressively increases the plasma concentration of morphine in parallel with increase in morphine dose if the patient has no pleural effusion, ascites or edema. In contrast, in patients with pleural effusion, ascites, or edema, the plasma morphine concentration was about half of that observed in patients who have a normal distribution volume. The rapid development of pleural effusion or ascites lowers the blood level of morphine (63).

Morphine sulphate continuous released suppositories (MS-CRS), administered every 12 hours, provide analgesia comparable to S.C. morphine and represent a reliable, non-invasive alternative method of pain control for patients unable to take oral morphine. This option is equally effective and simpler to institute for patients with a short life expectancy (64).

1.10.4 Spinal and intraventricular administration

Spinal administration of opioids, alone or in combination with local anesthetics, should be reserved for patients in whom systemic analgesic therapy is unacceptably or unmanageably toxic (22) or if there is little or no pain relief with increasing dosages of systemic strong opioids.

In some very selected cases, intraventricular morphine administration is indicated to alleviate intractable cancer pain, especially for patients with pain from head and neck cancers or from tumors invading the brachial plexus (65).

1.10.5 Conclusion on administration of analgesics

Advances in the management of cancer pain with opioids resulted from the development of slow- and sustained release tablets as well as novel alternative routes of drug administration (transdermal, buccal, transmucosal, subcutaneous, epidural and intrathecal) and drug delivery with intermittent and continuous patient controlled analgesia pumps. These different approaches make it possible to maximize the individualization of opioid therapy to obtain optimal analgesia while minimizing side effects, and provide convenient methods of drug administration (48).

Controversy continues to exist over the relative merits of the various standard and novel routes of administration and the indications for their use in the treatment of cancer pain. New routes of administration have become fashionable but often lack kinetic and clinical logic (66). Conflicting views about the usefulness and efficacy of these methods have resulted in considerable variations in practice, even among specialists in palliative care and pain management (26). The European Association for Palliative Care therefore set up a working group of experts to formulate recommendations for the use of morphine for cancer pain based on the available evidence (14). The oral route is the preferred one for administration of strong opioids, followed by the transdermal and subcutaneous routes.

All currently used approaches have demonstrated good analgesic efficacy and controllable adverse effects and have been instrumental in improving the quality of life when adequate analgesia has been achieved. There was and still is controversy as to whether the continuous infusion of strong opioids leads to more rapid development of tolerance than other routes (62, 63). Firm data to prove this are lacking and extensive clinical experience suggests that >90% of the patients who require an escalation in opioid dose to manage increasing pain have disease progression.

The choice of the route of morphine administration should mainly be guided by the needs of each individual patient. The location of the treatment will influence the choice of the analgesic. In the majority of cases, oral opioids are still the first choice but if the patient is no longer able to tolerate oral administration, for whatever reason, a number of factors must be considered and the availability of expertise and equipment is one factor which should not be neglected (67).

1.11 Hospital and home care

After the previous paragraphs it is clear that patients can be effectively treated for cancer pain in every health care setting thanks to the numerous analgesics and the different administration routes. Research has proven that symptom control at home can be as good as or even better than in the hospital. When physical, emotional and social parameters are considered, skilled care in the patient's own home is seen to be more effective. By far the majority of incurable cancer patients (about 70%) prefer to spend their remaining days in the comfort of their own home. At the beginning of the eighties many palliative caregivers, supported by many patients and their families, strongly believed that home is the preferred place of care for most terminal cancer patients (68). At the end of the nineties more and more experienced home care professionals became also available in Belgium to help families ensure that the dying process at home be as free of pain and as peaceful as possible. Nevertheless, it may happen that palliative care at home is no longer feasible for physical, social, economic or psychological reasons. At that moment the incurable patient himself or his family will, in consensus with his caregivers, opt for hospital admission for treatment, for temporary care, or to die. The relative weight of the different reasons why these patients enter hospital, how much time they spend there and how many of them can return home is not well studied. Can the hospital better offer these patients some effective treatment?

1.12 Strong opioids and elderly cancer patients

Many physicians, nurses and family members believe in clinical practice that elderly patients are at increased risk for opioid-induced side effects. Morphine therapy is therefore in these patients frequently postponed or given in too low dosage. Research in cancer pain treatment has given limited attention to the advanced age group. Because of the aging population, their number is progressively growing and they have a relatively high prevalence of cancer. We lack good scientific data for elderly patients concerning the real clinical efficacy in pain control, the tolerability of analgesic drugs and the handling of the side effects. Clinical investigation of these issues is therefore highly desirable since the number of elderly cancer patients will remain increasing in the next decades (6).

1.13 Strong opioids and tolerance

In 1986 the W.H.O. published the report "Cancer pain relief" to optimize cancer pain treatment. The report stressed that the greatest improvements in the quality of life of cancer patients could be obtained by applying the existing knowledge of pain and symptom control (13). By following these WHO guidelines, some investigators reported a very acceptable pain relief in 70-80% of patients (16, 17). Still seventeen years later, cancer pain treatment is far from optimal in the Belgian and Western health care systems. There are many reasons why physicians and cancer patients do not use strong opioids according to the internationally validated guidelines.

First of all there still is a worldwide lack of knowledge about pain pathophysiology, about the different analgesics and their pharmacokinetics. Thereby health caregivers did not really modify their attitudes in spite of the existing validated guidelines of the WHO.

Secondly there are the morphine myths. They suggest that strong opioids induce physical tolerance, depress the respiration, cause physical addiction and trouble the consciousness of the patients. All these myths restricted the use of strong opioids

for many decades, while strong scientific support for these myths was and is not present. On the other hand, I couldn't find published data about the percentage of patients with induction of tolerance, respiratory depression and confusion in cancer patients when they are treated according to the international guidelines.

Thirdly physicians have to give their patients a definite role in their own pain therapy with more freedom for the patients to adapt doses and administration of breakthrough medication (69).

Finally patients and caregivers are scared by the local legal regulations. The laws in many states discourage the optimal use of opioids via the sometimes difficult prescription policy (the limited dose per prescription, the administrative burden and controls) (70). A study found that nearly half the patients (48.8%) described their general practitioner as suspicious or skeptical towards opioid therapy (71).

Some patient organizations declared at the end of the 20th century that the time is ripe for professional accountability, including actions by medical disciplinary boards, when pain treatment is not adequately offered in the health care systems. I still agree in 2003 with the statement of Connolly in 1987: "What is needed now is not a stunning new understanding of pain pharmacology, but the consistent and rational application of what we already know. History will judge us harshly if we continue to fail to meet even this modest goal" (72).

We do not need other or better guidelines for opioids in cancer pain treatment and we cannot change the laws in many countries in a few years.

We have to optimize the physicians' and nurses' attitudes in cancer pain treatment by giving better pain treatment education, by giving practical training in pain therapy, by learning to use outcome measurements both by patients and caregivers and by looking for correct scientific data to assess the importance of the morphine myths.

1.14 Refractory symptoms in terminal palliative patients

Palliative care received some attention in West-European medical practice since ±1980 and progressively became available for many palliative patients in the last two decades. Even the most optimal pain treatment cannot always relieve all pain and suffering. These are the so-called "intractable" or "refractory" symptoms to standard palliative treatments. Refractory symptoms have to be differentiated from 'difficult to treat symptoms'. A difficult to treat symptom is refractory when after implementing the advice of several clinical experts the symptoms of the patient still cannot be relieved. A refractory symptom cannot be adequately controlled despite aggressive efforts to identify a tolerable therapy that does not compromise consciousness (73). Refractory symptoms are sometimes so overwhelming for patients, family and caregivers that they preclude a dignified terminal phase or dying process.

Palliative sedation can sometimes be indicated for these patients as an ultimate tool to control otherwise intractable symptoms in suffering patients. This is a controversial ethical topic since many years. Some authors have suggested that physicians use sedation to hasten death (74). Other authors have wondered why to sedate the patient if many patients and family members could ethically accept euthanasia when terminally ill patients have to suffer (75). The ethical debate moreover is intensified by the suggestion that sedation could be used as "slow euthanasia" (76).

1.15 Questions to be studied

In chapter II we analyze the data of the palliative cancer patients who were admitted to the hospital through an emergency procedure and for whom pain was the only or one of the dominant complaints. We evaluated the reasons for hospitalization, what the hospital could offer and what the outcome was for the patients.

Chapter III analyses the tolerance to TTS-fentanyl and rescue doses of morphine. The convenience for the patients, with a special focus on the elderly patients, and their compliance to the patches are analyzed.

Chapter IV studies the increase in opioid dose in function of time. The consumption of strong opioids is measured in a large number of patients treated for at least 3 months and at most 24 months. The importance of opioid tolerance in cancer pain treatment over a two-year period will be assessed.

Chapter V presents our experience with palliative sedation. How many symptoms remain refractory to modern effective pain treatment? Can palliative sedation relieve pain and suffering if pain treatment and other appropriate measurements fail and what are the ethical implications of palliative sedation? Is palliative sedation a true palliative tool or is it just a concealed method of euthanasia?

On the basis of the results obtained, we finally formulate some provisional conclusions with perspectives for future clinical research.

Chapter II:

Emergency hospital admission for pain in palliative patients.

2.1 Patients and methods

All palliative patients who entered the oncological ward of the Leuven University Hospital as emergencies were prospectively registered during a 3-month period. The different complaints and symptoms of the patients were prospectively recorded. The tumor type, all diagnostic, supportive and therapeutic measures taken in the hospital were registered. The length of the hospital stay was measured in relation to the different diagnostic and therapeutic activities performed and the destination upon discharge was recorded.

2.2 Analysis

This is a descriptive correlational retrospective study. Palliative cancer patients were at random prospectively registered during 3 consecutive months entering the hospital in emergency for pain. The absolute patient numbers are reported. The percentages of different groups of patients are referred to the total group of 67 patients (= 100%). The medians were calculated because the data were non parametric. The Fisher's Exact Test was used to calculate the differences between patient groups. The difference in hospitalization duration for oncological treated and patients that were just cared for was calculated with the t-test.

2.3 Results

Sixty-seven (54%) out of the 124 admitted palliative patients had pain as either the only or one of the main reasons for emergency hospital admission. These 67 patients with pain are the focus of this study.

2.3.1 Pattern of entrance into the hospital

Thirty-one patients (46%) were admitted via the emergency ward and 16 (24%) were sent from home immediately to the oncological ward. Ten (15%) patients were admitted via the hospital's outpatient department, 5 patients (7%) came via the day-care hospital and 5 patients (7%) via the radiotherapy department.

In patients coming straight from home (n = 48/67), there was equal distribution between those who decided autonomously (n = 23) to enter the hospital and those who were referred by the general practitioner (n = 25). For all patients in whom the general practitioner took the decision to request emergency admission (25/25), a referral letter was available. Seventeen out of 31 emergency ward patients and 11/16 patients coming directly from home had a written referral (=60%) from their general practitioner. The oncologists from inside the hospital (outpatient department and day-care hospital) sent in fifteen patients, and for 4 patients it was not clear who finally decided the admission.

For 44/67 patients (66%) a referral letter was available. The aim of the hospitalization by emergency was briefly mentioned in the referral letters while the respective analgesics and their doses were very rarely reported. Figure 1 shows that 51 (67%) patients entered during the working hours in the week and that only 2/67 patients in this study were admitted by emergency to the hospital during the weekend. A high number of emergency admissions were seen on Monday (27%), there were less on Tuesday (21%) and a steady state was reached from Wednesday (15%) to Friday (18%).

2.3.2 Demographics

The demographic data are presented in Table 1. There is a clear female/male ratio of 2.2. This is mainly caused by the large number of breast cancers (n = 24), which constitute the most important group of patients in the Oncology Department. Lung cancer is the second most frequent malignancy in this patient

group. All the other tumor types (head & neck, gastro-intestinal tract, urological, gynecological cancer, lymphoma, sarcoma and brain tumor) are nearly equally represented.

Figure 1: Distribution of the number of patients admitted in emergency to the hospital in function of day and hour of hospital entry.

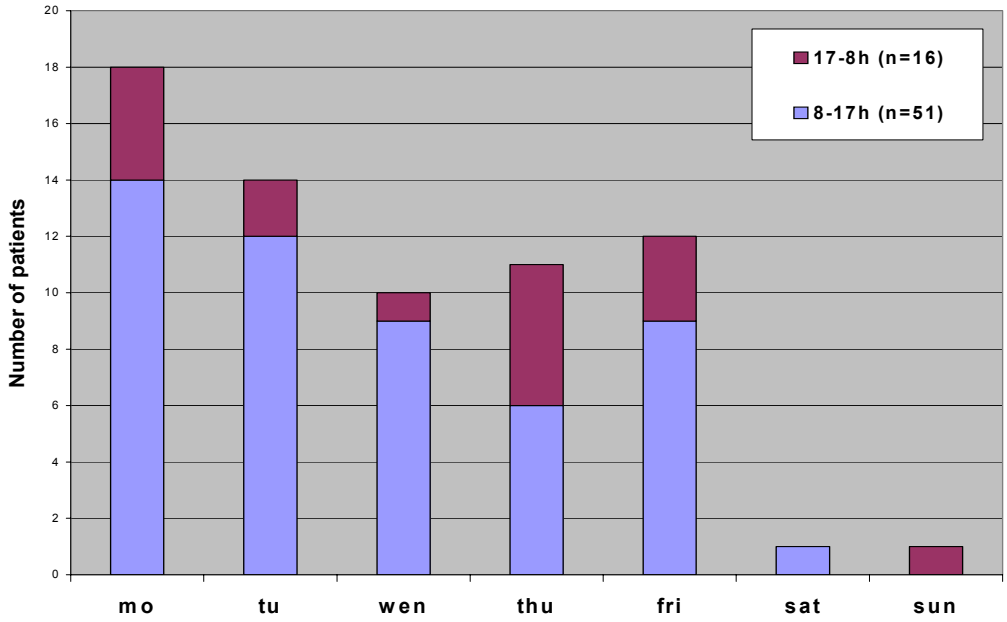


Table 1: Demographic data

Male N= 21 Female N= 46	Age: median = 61.66 y median = 54.6 y	Age: range 42-88 y range 19-86 y
Primary cancer site N		
Breast 24 Lung 11 Head & neck 5	Gastro-intest. tract 5 Urological 5	Lymphoma 5 Sarcoma 4 Brain 3

2.3.3 Clinical symptoms of the patients

Pain was the inclusion criterium for this study and thus was present in all 67 patients. Pain was the only symptom on the day of admission in 17/67 (25%) patients. The other symptoms and complaints (Table 2) were never the only reason for admission by emergency; there always was a combination of pain with 1 (n = 24/67 or 36%), 2 (n = 22/67 or 33%) or maximum 3 (n = 4/67 or 6%) other symptoms or complaints.

Besides pain, the most frequent other symptoms or complaints were: cachexia (n = 20/67), dispose (n = 12/67), need for increased physical care (n = 15/67), fever (n = 9/67), nausea/vomiting (n = 8/67), gastro-intestinal obstruction or diarrhea (n = 5/67), social reasons (n = 4/67) and vena cava superior syndrome, hemorrhage and anxiety (n= 2/67). The remaining symptoms were reported in only one patient (ascites, confusion, edema in legs, anemia, neurological deficit and phlegmonia).

Table 2: Symptoms and complaints causing hospital admission by emergency.

Symptoms & complaints	N	Symptoms & complaints	N
Pain	67	Vena cava superior syndrome	2
Cachexia	20	Haemorrhage	2
Dyspnoea	12	Anxiety	2
Additional care needed	15	Ascites	1
Fever	9	Confusion	1
Nausea & vomiting	8	Oedema in the legs	1
GI-obstruction /diarrhoea	5	Anaemia	1
Social reason	4	Neurological deficits	1
		Phlegmonia	1

2.3.4 Reason for hospital admission and hospital activities

The patients were referred, or entered the hospital for additional nursing and medical care (N = 15; 22%), for diagnostic work up (N = 41; 61%) or for treatment (N = 59; 88%). Table 3 shows that the referrals were very realistic and correctly implemented by the hospital, because what really was done is exactly what the patients were referred for: 21% of the patients only received care, 68% underwent diagnostic procedures and 92% received some form of therapy.

Table 3: Reasons for referral and what effectively is done in the hospital

	Reason for referral		What effectively is done?	
	N	%	N	%
Nursing care	**15**	22	**14**	21
Diagnostic procedures	**41**	61	**46**	68
Therapy	**59**	88	**62**	92

2.3.5 Treatments done in hospital

All treatments applied in hospital are summarized in table 4. Analgesic treatment was adapted or started in 39/67 (58%) patients. This group can be divided into two groups in which 25/39 (64%) patients received "hospital specific treatments" and the other 14/39 (36%) patients received non-hospital specific treatments. The hospital specific treatments for 25/39 patients were specialized or permanent need for nursing (n=9), radiation therapy (n=8), chemotherapy (n = 7), disphosphonates, referral to surgeon, blood transfusion, parenteral feeding, ascites puncture, thoracic drainage, a Port-à-Cath implantation.

There were 21 non-hospital specific treatments done in the 14/39 patients and for 5/25 patients from the first hospital specific treatment group: rectal clysma, placement of an urinary catheter (n=2), administration of antibiotics (n=3) or

corticosteroids (n=3), adaptation of medical pain therapy (n=9), administration of anti-emetics or oxygen and delivery of wound care (each n=1).

Although 14/39 patients didn't really need the hospital infrastructure for their treatment, 11/14 of these patients had some diagnostic procedure (X-ray, endoscopies or functional examination for diagnostic reasons). Only 3/14 patients were in the hospital without requiring any hospital-related diagnostic or therapeutic procedure.

Analgesic drug treatment was not adjusted during hospitalization in 28/67 (42%) patients. Twenty-four of these 28 patients (86%) needed hospital specific treatments while 4/28 didn't. The hospital specific treatments were: additional nursing care (n=4), radio- (n=9) and chemotherapy (n=6), disphosphonates (n=1), parenteral feeding (n=1), placement of a Cantor drain (n=1), rehydratation (n=2) and placement of a cystofix (n=1). Ten non-hospital specific treatments were done in 2/28 patients without a hospital specific treatment and in 8/24 patients from the hospital specific group: hormonal treatment (n=4), antibiotics (n=3), anti-coagulation (n=1) and corticosteroids (n=2). In the 4/28 patients who didn't use any hospital specific treatment, 1 patient didn't use neither any diagnostic nor a therapeutic or care facility of the hospital and this patient left the hospital 1day after admission. Two patients underwent only diagnostic procedures and they were advised against further antitumoral treatment, in one patient a symptomatic treatment with corticosteroids was started. The fourth patient started hormonal treatment after diagnostic work-up.

There were 57 hospital specific treatments (32/39 and 25/28) and 31 non-hospital specific treatments (21/39 and 10 /28) performed in the 67 patients that were admitted by emergency for pain. There were only 3/39 and 1/28 patients admitted by emergency who didn't require any diagnostic nor therapeutic hospital specific procedure. There is no statistical significant difference in the hospital specific treatments between the patients who needed and the patients who didn't need adaptation of analgesics ($p = 0.36$ Fischer's Exact Test).

Table 4: Hospital specific treatments and non-hospital specific treatments given during the hospitalization.

	Adaptation of analgesics (N = 39/67)		No adaptation of analgesics (N = 28/67)		Hosp. Specific. Treatment
	Hosp. Spec. Treatment (N= 25/39)	Non. Hosp Spec. Tr. (N=14/39+ 5/25)	Hosp. Spec. Treatment (N = 24/28)	Non Hosp. Spec. Tr. (N= 2/28 + 8/24)	
Additional care	**9**		**4**		**13**
Radiotherapy	**8**		**9**		**17**
Chemotherapy	**7**		**6**		**13**
Diphosphonates	**1**		**1**		**2**
Referral to surgeon	**1**				**1**
Blood transfusion	**1**				**1**
Parenteral feeding	**1**		**1**		**2**
Ascites puncture	**2**				**2**
Cantor drain			**1**		**1**
Port-à-Cath	**1**				**1**
Thoracic Drain	**1**				**1**
Rehydratation			**2**		**2**
Hormonal treatm.				**4**	
Rectal clysma		**1**			
Urinary catheter		**2**	**(Cystofix) 1**		**1**
Antibiotics		**3**		**3**	
Anti-coagulation				**1**	
Corticosteroids		**3**		**2**	
Change analgesic therapy		**9**			
Ant-emetics		**1**			
Oxygen		**1**			
Wound care		**1**			
Total	**32**	**21**	**25**	**10**	**57**

2.3.6 Duration of hospitalization

Table 5 shows the median hospitalization duration in function of the treatment that was given. Chemotherapy patients remained in hospital for a median duration of 16.6 days, while the 17 patients who were irradiated had a median hospitalization of 15 days. Whether medical pain treatment was adjusted (n = 39/67) or not (n = 28/67), the median duration of hospitalization in both situations was nearly 11 days (respectively 10.7 and 10.5 days). Hospital intervention restricted to nursing care and adjustment of analgesic drugs, without chemo- or radiotherapy, resulted in a median hospitalization of 9.1 days. When only the analgesic treatment was adapted without need for nursing care, without chemo– or radiotherapy, then the median hospitalization time was 7 days. The shortest stay was noted for patients to whom only additional care was offered, without chemo- or radiotherapy and without change in analgesic drug therapy. For these patients, a median hospital stay of only 5.5 days was registered. There is a significantly longer hospitalization for patients treated with chemo- or radiotherapy compared with all the others (p= 0.0003 t-test)

Table 5: Mean duration (days) of hospitalization in function of therapy.

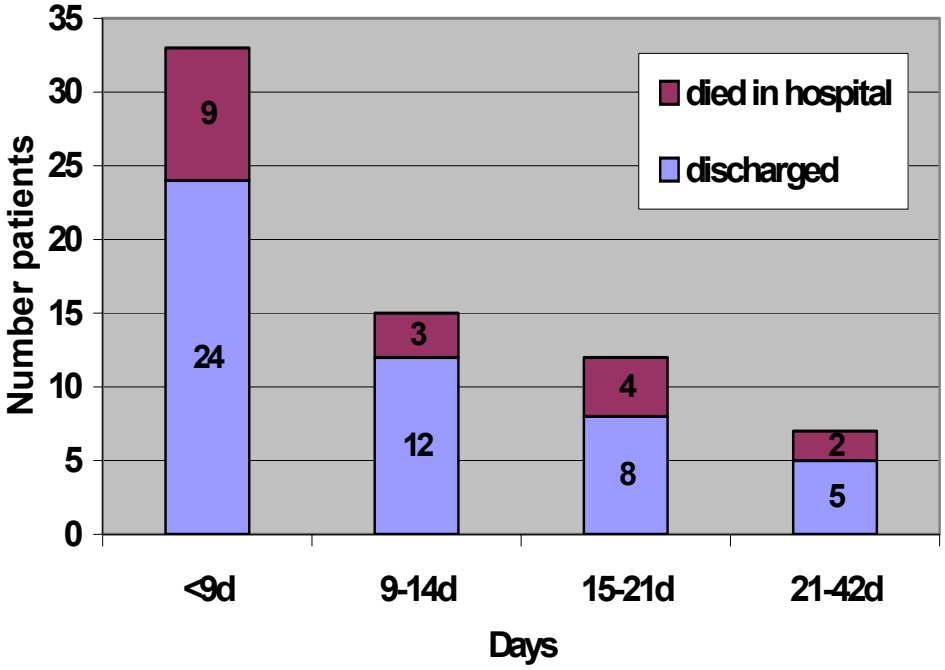
Hospital treatment	Hospitalization duration (d)	Patients(N)
Chemotherapy	**16.6 (range 4-34)**	**13**
Radiotherapy	**15 (range 1-37)**	**17**
Adaptation of analgesics	**10.7 (range 1-34)**	**39**
No adaptation of analgesics	**10.5 (range 1-37)**	**28**
Care + pain treatment	**9.1 (range 1-20)**	**8**
Analgesic treatment	**7 (range 1-34)**	**15**
Other *	**6.4 (range 1-15)**	**12**
Only additional care	**5.5 (range 3-8)**	**2**

*Corticoids (n=2), anticoagulants, cystofix, disphosphonates, rehydratation, Cantor drain, parenteral nutrition.

2.3.7 Patient outcome

Within 8 days could 24/67 patients return home while 9/67 others died in the hospital (together 49%), 12 patients left the hospital after 9-14days and 3 patients died in the hospital during this second week (together 22%). Eight patients remained 15-21 days while 4 others died in this third week (together 18%). Finally, 5 patients were hospitalized for 21-42 days while 2 other patients died during this hospitalization (together 10%) (Figure 2). All the discharged patients (49/67=73.1%) returned home except one patient who moved to a palliative care unit (n = 1); 18/67(=26.9%) patients died in the hospital after a mean stay of 11 days.

Figure 2: Number of patients that died or were discharged per week after hospital admission in emergency.



2.4 Discussion

The emergency ward of the hospital functions as a crisis center for all the problems of the home cared palliative cancer patients that can't be solved at home. It is striking to see that these patients rarely enter during the weekend when the available professional care at home is reduced (Figure 1). The patients mainly came in from Monday to Friday, with a higher frequency on Monday and Tuesday. The increased admittance in emergency at the beginning of the week could suggest that the patients would like to first get some advice from their general practitioner before they definitely decide to come to the hospital. This is also reflected by the 25/25 referral letters when the general practitioner sent the patient in emergency to the hospital, but also by the high number (19/42) of referral letters when somebody else was the driving force leading to hospitalization. The total of referral letters is 44/67 (=66%). This proves the important function of the general practitioner as " health care manager" for palliative cancer patients.

It is possible that during the weekend the family members are more involved in caring for or visiting the patient than on week days and that they become convinced that further home care is inadequate, or too difficult for the patient and the family, or even becomes impossible. This family perception and initiative can add to the relative excess of emergencies on Monday and Tuesday.

All cancer types are responsible for emergency admissions in the same relative proportion as they occur in our oncology department (Table 1). No specific tumor type seems more eligible than others for emergency hospital admission.

Poorly controlled pain was the main reason for admission in 67/124 (59%) emergencies in advanced cancer patients during the 3 month study period (Table 2). This high frequency is confirmed in the literature. Pain (46-71%) and general

weakness or fatigue (43-82%) are the most frequent symptoms in advanced cancer patients. A survey of 1102 consecutive admissions to a specialty hospital devoted to the care of patients with advanced cancer revealed that on presentation 73% had pain and 38% of them even had severe pain (9). In our study, pain was the sole symptom responsible for 17/67 (25%) emergencies. This fits well with the published data. The family and the general practitioner find that the main reason to refer a patient to a palliative care program is pain (29%), followed by terminal care (17%), home support (17%), psychosocial support for the patient alone (10%), psychosocial support for both patient and family (10%) or for the family alone (10%) and management of other symptoms (7%) (12). In this study, 50/67 (75%) patients had 1 to 3 symptoms other than pain at hospital entry. This proves that in the majority of advanced cancer patients pain is not the sole symptom that has to be treated, although it is the most frequent one and the symptom that has the most impact on the care of palliative patients. Pain assessment and pain relief measures should be a priority for all cancer caregivers during both active cancer treatments and the palliative care period. Palliative care cannot be limited to just pain treatment; adequate control of the other symptoms is essential as well.

Better communication between physicians concerning pain treatment in the different palliative care settings will probably shorten the time that is necessary to relief cancer pain for individual patients.

Eighty-eight percent of the patients were referred to or entered the hospital for therapy (Table 3) and 92% of the patients received some treatment (Table 4), of whom 73% (25/39 + 24/28) actually received hospital specific therapy. It seems astonishing that in 36/67 (53.7%) of these far advanced and no longer treated palliative patients an anti-tumor treatment was re-established: 17 radiotherapy, 13 chemotherapy, 4 hormonal therapy and 2 disphosphonates. In the Memorial-Sloan-Kettering Cancer Center an etiological treatment was started in two thirds

of the patients with “refractory pain” after a diagnostic procedure (28). This proves that medical decision making in cancer patients also in the palliative care phase is a dynamic process. New pain patterns ask for new deliberations concerning etiological or symptomatic treatment. Many pain symptoms and syndromes in cancer patients can be alleviated by anti-tumor therapy. A total of 57 hospital-specific treatments were performed in the 67 patients and in addition 31 non-hospital specific treatments were initiated (Table 4). This holistic approach is only possible when enough experts from different disciplines are consulted soon after the patient enters the hospital. It is the aim to discharge the palliative patient as soon as possible for further home care after effective treatment. In this study 35.8 % of the patients were back home in less than 8 days and 53.7% were home within 14 days while respectively 13.4 and 4.4% of the patients died in the first and second week of hospitalisation (Figure 2). This implies that 71.6% of the emergency patients are already discharged out of the hospital at day 15. The more treatment that is required, the longer the patients are hospitalized. Patients treated with chemo- and radiotherapy stayed statistically significantly longer in hospital (15-17d.) than others ($\leq$10d.) (Table 5). This suggests that the hospital caregivers were aware of and considered the wish of the palliative cancer patients to return to the home care system as soon as possible. The weakness or fatigue, the pain or the deteriorated general condition in most patients may not allow to perform the more labor intensive diagnostic work-up (68% needed these) and treatments (73%) on an ambulatory basis.

Only 4/67 (6%) of the patients was hospitalized without need of the diagnostic or therapeutic infrastructure of the hospital. This indicates that the home caregivers and the patients have realistic expectations on what the hospital infrastructure and expertise can provide. Sometimes it is suggested that the home caregivers transfer their terminally ill patients to the hospital just before dying, maybe as a result of insufficient control of physical symptoms and psychological pressure. There is no basis for this statement in this analysis since only 3/67 patients (4.5%) died

within 24 hours, another 4 patients (6%) died during the first week of hospitalization and the other terminally ill patients (11/67 or 16%) died between 8 and 37 days after emergency admission.

Many caregivers are convinced that palliative care is the exclusive responsibility of the home care and that hospitals have to implement all available scientific knowledge to cure diseases and to maintain patients' health as long as possible. However the home care needs support from and close cooperation with the acute hospital as a back-up system. Sometimes the hospital has to take over the care, for a short time or sometimes permanently, when home caregivers and the family or friends are no longer able to provide adequate support due to the intensity or complexity of the symptoms or for social reasons. This study provides evidence for the complementary role and effectiveness of rapid relief of symptoms in an acute oncological ward, when home care can no longer cope with refractory pain or other symptoms in advanced palliative cancer patients.

Acute oncological hospital wards have a twofold task for advanced palliative cancer patients who enter in emergency. They have to provide well organized diagnostic and therapeutic procedures of limited duration to relieve symptoms, as far as possible, by a range of specific hospital based treatments, allowing the home care team to take over the further palliative care as soon as possible. For those patients who will die during the hospitalization (18% in our analysis), they have to provide effective pain and symptom control in an environment where social, psychological and spiritual issues are considered, to guarantee a peaceful death with dignity, the patient being surrounded by his relatives and competent professional support where necessary.

2.5 Conclusion

Cancer pain is frequent (>50%) in palliative patients and is the only symptom responsible for an emergency hospital admission in many patients (25%). But there is more than pain, many patients have 1 to 3 additional symptoms or complaints , that also need to be relieved as quickly and as well as possible. This big challenge is not feasible for one single discipline. Nurses, physicians of different specialties, psychologists, clergy and social workers have to cooperate to relieve the patient and his family as much as possible. This study shows the wide variety of therapeutic options that had to be offered to 67 far-advanced palliative cancer patients admitted to the hospital in emergency for pain and other symptoms. An etiological treatment has to be started where possible.

The acute wards in the cancer hospital have an important task to provide rapid diagnostic and therapeutic strategies for the many far-advanced palliative cancer patients. Fifty-three percent of the patients did return home within 2 weeks after emergency hospital admission for pain and other symptoms. Although they are already palliative patients, many of them will still profit from newly started anti-tumour treatments with chemo-, radio- or hormonal therapy. Assessment and adaptation of symptomatic pain treatment has frequently to be done as well.

Pain and symptom control are very frequent palliative issues with a heavy emotional, social and financial burden for the patient and the community (management, staff, investment and costs). The knowledge of the palliative principles, the attitude to manage these, must form the basis for good clinical practice by all caregivers, both in the hospital and in the home care. Quick and effective management of these problems is a challenge for all concerned. People who are responsible for medical education and management have to consider these issues.

Chapter III:

Longitudinal follow-up of TTS-fentanyl use in patients with cancer pain: results of a compassionate use study with special focus on elderly patients

This chapter has been published in
Current Medical Research and Opinion 2002; 18: 488-498.

3.1 Patients and Methods

3.1.1 Study design

Adult patients with cancer pain caused by the presence of a histologically confirmed and incurable malignant disease and for who even palliative systemic anti-tumor therapy no longer was available, were eligible for this open-ended Belgian multicenter evaluation of TTS-fentanyl. Patients were to take opioid analgesia according to step III of the WHO analgesic ladder (77) and to have an estimated survival of at least 3 months. Excluded from the study were patients with a history of allergy to opioids, a history of narcotic abuse prior to their diagnosis of cancer, active skin disease precluding application of the transdermal system, or a clinically relevant history of pulmonary failure (CO_2 retention), renal dysfunction (serum creatinine > 2.0 mg/dl) or liver dysfunction (serum bilirubin > 2.0 mg/dl). The study was conducted in accordance with the Declaration of Helsinki. Full approval of the protocol was obtained from the local independent ethical committees. All patients provided informed consent before study entry.

Enrolled subjects were first stabilized on oral morphine to obtain adequate pain relief, except for patients already taking TTS-fentanyl or oral morphine and patients unable to continue taking oral morphine (e.g. swallowing problems, unacceptable morphine-related constipation). These patients entered the study without prior stabilization. Patients using opioids other than oral morphine and TTS-fentanyl prior to study entry were converted to oral morphine according to the standard "opioid analgesic conversion table" (78) and titrated to a stable dose.

After stabilization on oral morphine, patients were switched to an equi-analgesic TTS-fentanyl dose, according to the "P.O. morphine sulphate to TTS-fentanyl Conversion Scheme" with a conversion ratio 150:1 (79). In addition to the study drug, patients used immediate release morphine on an as-needed basis as rescue

medication for incident or breakthrough pain. Oral morphine in a dose of 1/12 to 1/6 of the daily equivalent TTS-fentanyl maintenance dose in a concentration of 1 or 5 mg/ml. solution could be taken every 4hr. if pain occurred.

Dose adjustments were permitted at each patch renewal (every 3 days). The TTS-fentanyl dosage titration was performed with stepwise increments (or decrements) of 25 µg/hr., based on patients' daily supplemental analgesic requirements, balancing adequate pain control with an acceptable level of side effects and a minimal need for supplemental rescue medication.

Concomitant use of fixed doses of non-steroidal anti-inflammatory drugs (NSAID's), paracetamol or aspirin was allowed as far as the initial dose at study entry remained unchanged. Treatment initiation or dose adaptations were only permitted if judged absolutely necessary by the investigator. This also applied to potential central nervous system depressants such as anxiolytics, hypnotics and tricyclic antidepressants. The use of anti-emetics, antihistamines and laxatives was not restricted.

3.1.2 Assessments

Patients were evaluated periodically at least every 28 days. It was the aim in this study to keep the pain equal or below 3.5 on a VAS-pain scale from 0 to 10 for all patients. TTS-fentanyl dose adjustments and rescue morphine requirements were recorded at each follow-up. Drug tolerability was assessed by documenting all adverse events and side effects. The occurrence of constipation was reported using a 3-point scale (mild-moderate-severe) with particular attention to the use of laxatives. Reasons for study discontinuation were reported. In addition, the convenience of the patches was evaluated using a 4-point scale (unsatisfactory, moderate, good, and excellent).

3.1.3 Analysis

Descriptive statistics were performed regarding baseline characteristics and periodic assessments. The last documented visit was defined as the individual study endpoint. The type and incidence of all adverse events recorded during the study were registered, with special attention to reasons for study discontinuation.

The Safety population consisted of patients that received at least one dose of TTS-fentanyl. The Evaluable population was defined for analytical purposes and consisted of subjects who took at least 1 dose of study medication and had information available from at least 1 on-treatment visit, in addition to the baseline data. In both populations, two subpopulations were compared to the whole population: the elderly patients, consisting of all subjects of 60 years and older, and the opioid naïve patients, consisting of patients who started directly on TTS-fentanyl without prior step-up pain management with weak or strong opioid analgesics, skipping the second step of the WHO analgesic ladder. For sample sizes smaller than 20 patients, no analyses were performed.

The drug doses were non-Gaussian distributed. Most patients used relatively low doses of opioids while there were few patients treated with huge doses of opioids. Therefore the medians are reported, the mean doses are given for the completeness of the information, where this is appropriate. When data were parametric (age distribution), the means are given.

3.1.4 Medication

TTS-fentanyl (Durogesic® patch, Janssen Pharmaceutica), a transdermal opioid delivery system, releases fentanyl from a reservoir through a rate-limiting membrane to the skin and a depot of the drug concentrates in the subcutaneous tissues. After approximately 12 hours steady-state plasma fentanyl concentrations are reached and are maintained for about 72 hours. Fentanyl patches are available in 25, 50, 75, and 100 µg/hr. dosages. Multiple patches are applied at the same time if doses above 100 µg/hr. are needed.

3.2 Results

3.2.1 Subject enrollment and reasons for discontinuation

Between June 1994 and September 1997, a total of 663 patients with a wide range of malignancies were recruited by 54 Belgian investigators and enrolled in this multicenter study (Table 6). Of these, 661 patients took at least 1 dose of study medication (Safety population).

Table 6: Number of patients in each population.

	Safety Population	**Evaluable Population**
	≥ 1 dose of trial medication	≥1dose of trial medication
		Baseline data
		≥1 on-treatment visit data
Total	n = 661	n = 455
Elderly	n = 341	n = 235
Opioid naïve	n = 55	n = 30

Despite an estimated survival at inclusion of at least 3 months, more than one third of patients (37%, n=246) dropped out of the study during the first month of therapy. The number of patients further declined steeply, leaving 24% (n=162) of patients included after 3 months and 10% (n=65) after 6 months. The major reason for premature discontinuation of the study was the occurrence of death (61% of patients, n=397), mainly related to cancer progression. Adverse experience was indicated as one of the reasons for study discontinuation in 286 patients, mostly reported in combination with the previously mentioned cancer death (n=241), together with other reasons for withdrawal (n=27) or as unique reason (n=18).

Other reasons for withdrawal from the study were insufficient response (n=111), loss to follow-up (n=50), uncooperativeness (n=21) and consent withdrawal (n=3).

3.2.2 Demographics and baseline characteristics

Both genders were equally distributed over the study population (male/female ratio = 1.1). Patients' mean age (± standard deviation) (SD) was 59 (± 13) years, ranging from 18 to 91 years. More than half of the patients (n=341 or 52%) were 60 years or over. The mean (± SD) age of these elderly patients was 69 (± 7) years.

A total of 455 patients had data available at baseline and at least 1 on-treatment visit (Table 6). In these patients (=Evaluable population), tumor history, previous and concomitant therapy, treatment duration and applied doses were assessed.

3.2.3 Tumor history (Evaluable population)

Primary tumors were most frequently localized in the gastrointestinal tract (n=97; 21%), followed by breast (n=79; 17%), lung (n=51; 11%) and prostate (n=41; 9%). The median interval between diagnosis of the primary tumor and study inclusion was 18 months.

3.2.4 Previous therapy and concomitant therapy (Evaluable population)

In the period of 2 weeks prior to study entry, analgesic therapy mainly consisted of strong opioids, often associated with non-opioid analgesics. Morphine intake was present in the majority of patients (89%) but also totally opioid naïve patients were included. Of 55 opioid naïve patients who entered the study, 30 patients were evaluable at baseline and had at least 1 on-treatment visit (6.6% opioid naïve patients in the Evaluable population). Paracetamol was the most frequently used

non-opioid analgesic, taken as a single preparation (11%) or combined with codeine (11%); approximately 15% of patients used NSAID's.
During the study, patients often used paracetamol, alone (41%) or combined with codeine (11%) to supplement pain control; NSAID's were taken by 31% of patients. Antidepressant intake was found in 7% and anticonvulsants in 5% of patients.

3.2.5 TTS-fentanyl treatment and rescue morphine use (Evaluable population)

3.2.5.1 Conversion from oral morphine to TTS-fentanyl at baseline

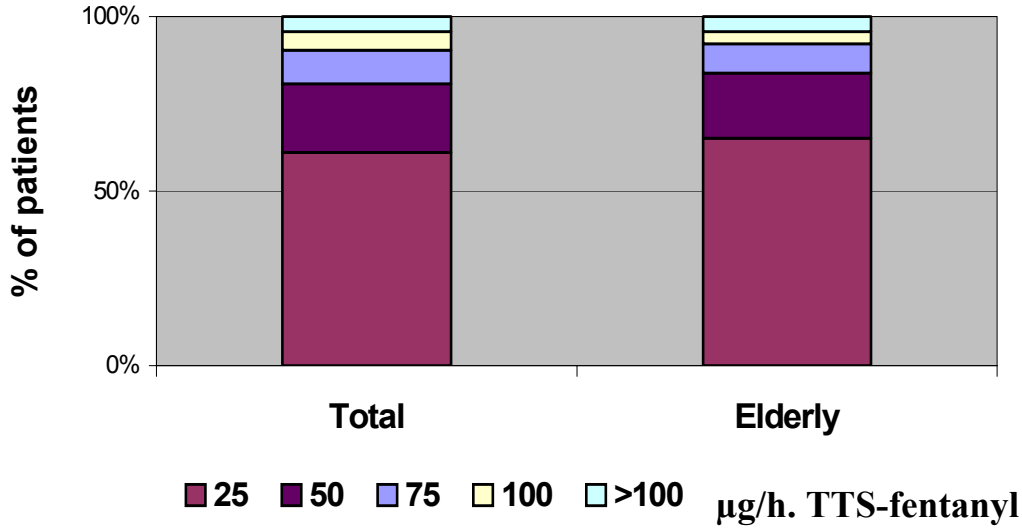
Information on the precise daily morphine equivalent dose at study entry was available for 75% of patients; the median (95% CI) dose was 120 mg/day (90-120 mg/day). More than 85% of these patients took daily oral morphine doses higher than 40 mg. Patients were converted to equi-analgesic TTS-fentanyl doses while continuing the use of rescue morphine for breakthrough pain. Most patients (61%) started therapy at the lowest dosage of the patches (25 µg/hr.) but 29% of patients were directly converted to higher TTS-fentanyl doses of 50 or 75 µg/hr. In 10% of patients therapy was initiated at 100 µg/hr. or higher (Figure 3). The median baseline TTS-fentanyl dose (95% CI) was 25 (25-25) µg/hr.; the mean was 46.6 µg/hr., ranging from 25 to 800 µg/hr.

3.2.5.2 Elderly patients

Morphine doses at study entry were only slightly lower in the group of elderly patients (median morphine dose (95% CI) of 100 mg/day (70-120)) compared to the whole Evaluable population with a median morphine dose of 120 mg/day (90-120). We found in the elderly that the older the patient, the lower the morphine dose that was applied. The baseline morphine use in the 60-69 age group (median dose of 120 (80-140) mg/day; n=99) was still comparable to the total Evaluable population, it was clearly lower in the group of patients aged 70-79 years (median daily dose of

90 mg/day (60-120); n=62) and in the group of patients of 80 years and older (median dose of 60 mg/day (30-120); n=16). However the number of patients in the subcategory of 80 years and older was already relatively small at baseline.

Figure 3: Percentage of patients (total group and ≥60 years) in the Evaluable population, receiving the various initial median doses of TTS-fentanyl (µg/hr).



The median TTS-fentanyl baseline dose (95% CI) used in the elderly patients was 25 µg/hr. (25-25), comparable to the total patient group, but less frequently extremely high individual start doses were found (min-max: 25-225 µg/hr). A total of 27% of elderly patients initiated TTS-fentanyl therapy at dosages of 50 to 75 µg/hr, and 8% at 100 µg/hr. or higher (Figure 3). While the median doses of the elderly were comparable to the total group, the mean TTS-fentanyl dose at baseline was 46.5 µg/hr. in the 60-69 years age group, 38.6 µg/hr. in the 70-79 years age group and only 29.5 µg/h. in the group of patients of 80 years and older. This reflects that older patients used lower mean TTS-fentanyl start doses which is in accordance with the lower morphine doses used at study entry in this age group.

3.2.5.3 Duration of the treatment phase

The duration of treatment of patients who entered the study showed large inter-individual variations ranging from a few days to 2½ years. In the Evaluable population (n = 455), the median (95% CI) duration of the TTS-fentanyl treatment phase was 81 days (range 70-90).

The data regarding the duration in the elderly patients (n = 235 and median duration of 76 days (range 62-90)) showed that tolerability of TTS-fentanyl in long-term therapy in the elderly patients was similar to the whole Evaluable population. In contrast, the median duration of the treatment phase was longer in the opioid naïve patients (107 days, with a range of 56 to154).

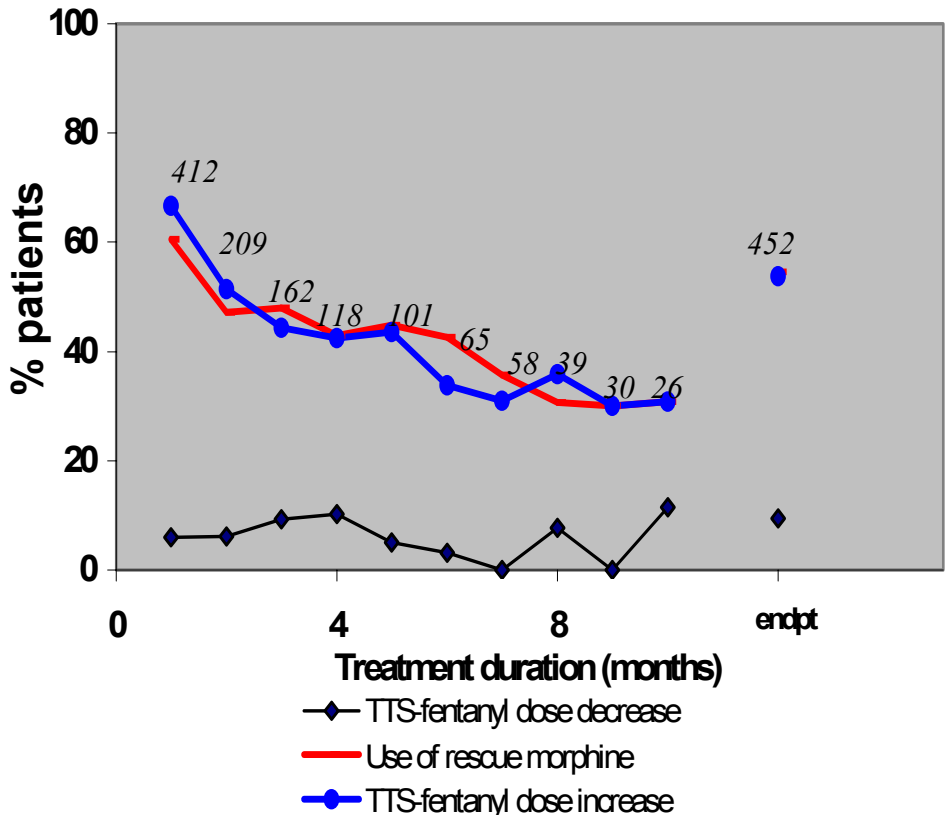
3.2.5.4 TTS-fentanyl dosage and use of rescue morphine over time.

TTS-fentanyl dose adjustments, relative to the previous treatment period, were recorded at each 4-weekly visit. The use of morphine solution, intended to treat breakthrough or incidental pain during the different study intervals, was documented in addition.

The median (95% CI) dose of rescue morphine used was 20 (10-30) mg/day at month 1 and 10 [0-20] mg/day at endpoint. If the rescue morphine doses were 60 mg/d. or higher in the individual patients, then the next TTS-fentanyl application was incremented with 25µg/hr.

TTS-fentanyl dose adjustments are given in Figure 4. It shows that dose increases of TTS-fentanyl were most frequent at the beginning of the study (67% of patients at month 1 visit) when the dropout rate related to disease progression also was highest. During the month prior to individual study endpoints, 54% of patients needed TTS-fentanyl dose increments. A rather similar course was found for the use of rescue morphine with 61% of patients using morphine doses during the first month of treatment, and 55% during the month prior to individual study endpoints.

Figure 4: Percentage of patients (n = 455 at baseline) who needed TTS-fentanyl dose increments, TTS-fentanyl dose decrements or who used rescue morphine during the previous treatment month in the Evaluable population. The right point (endpoint) corresponds to the last documented treatment month for all patients, independent from the duration of the therapy. The values in italic represent the total number of patients evaluated at each time point.



Dose decreases for TTS-fentanyl were relatively rare and were only seen in 6% of patients after 1 month of treatment and in 10% at the individual study endpoints. The median (95% CI) TTS-fentanyl dosage at endpoint was 100 (100-100) µg/hr. in this population, ranging from 25 to 950 µg/hr. The interpretation is biased by the

non-Gaussian distribution of TTS-fentanyl dosing in cancer pain management and confounded by the high initial patient dropout rate.

Therefore mean dosages for the total group and for the various elderly age groups are given in Figure 5 to illustrate that dose increases were most common during the first treatment month, slowly increased until month 4 but stabilized by month 5. In the different primary tumor groups, a similar time course of TTS-fentanyl dosage was found. Figure 6 represents these data per primary tumor class, insofar as more than 20 patients were available.

Figure 5: Mean TTS-fentanyl dose (± SD) in µg/h. in the Evaluable population in function of age and time. The right point (endpoint) corresponds to the last documented treatment month for all patients, independent of the duration of therapy. The values in italic represent the total number of patients evaluated at each time point.

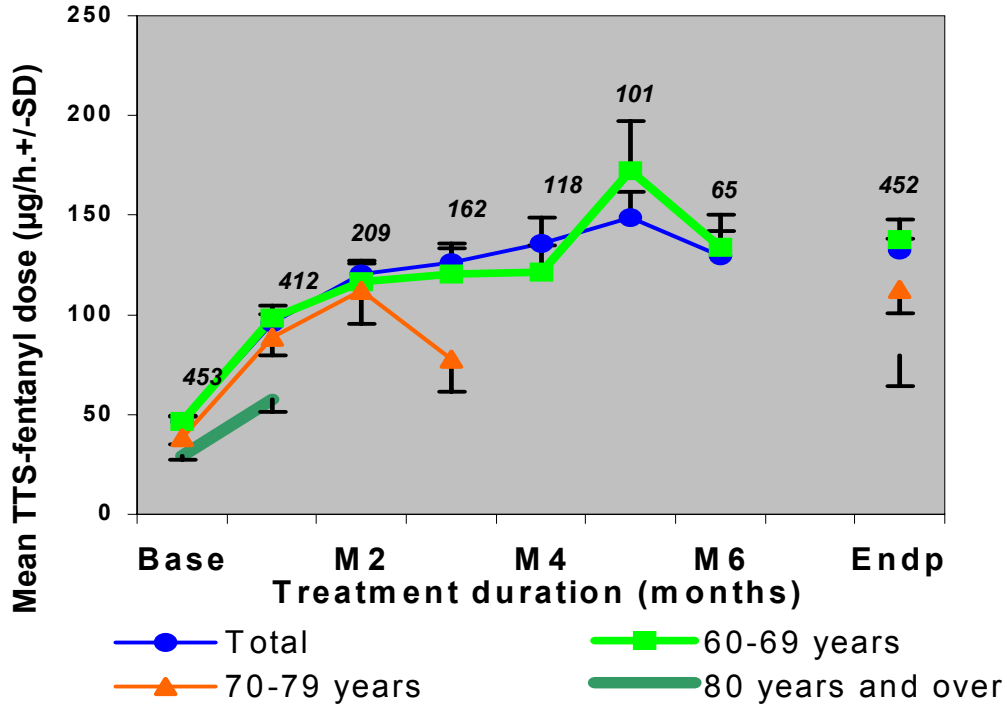
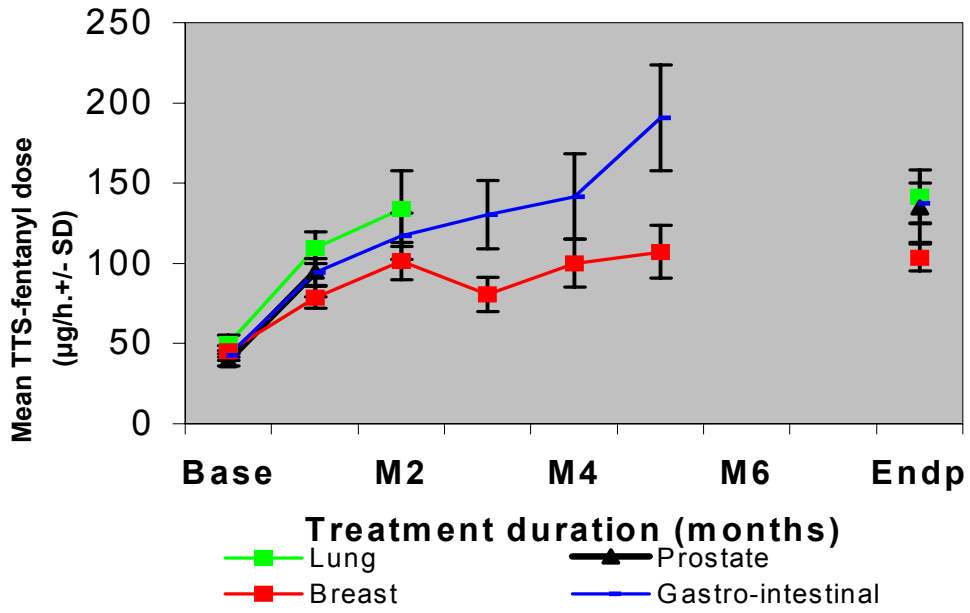


Figure 6: Mean TTS-fentanyl dose (± SD) during long-term therapy per primary tumour class in the Evaluable population. The right point (endpoint) corresponds to the last documented treatment month for all patients, independent of the duration of therapy.



3.2.5.5 Elderly patients

The time patterns of TTS-dose adjustments and use of morphine for breakthrough pain in the elderly patients were comparable to the total evaluable patients (data not shown). TTS-fentanyl dose increases were found in 68% and 54% at month 1 and at patient individual study endpoint respectively. Dose decreases were found in only 4% and 9% respectively.

Elderly patients from the subcategory of 60 to 69 years (n=130 at baseline) showed mean TTS-fentanyl dosages over time comparable to the total Evaluable population.

In the 70-79 age group (n=83 at baseline) and in the group aged 80 years and over (n=22 at baseline), lower mean TTS-fentanyl dosages were found respectively at month 3 and 1(Figure 5). The number of patients in these age subcategories was already limited and was still rapidly decreasing during the first months of the study; data are only shown for sample sizes of 20 patients and more. Taking into consideration the wide range of doses of TTS-fentanyl applied (25-500 µg/hr), the dose reduction that occurred in the 70-79 year age group at month 3 (Figure 5), should be interpreted with caution as only 20 patients were involved at this time point. The death of 1 or 2 high dose fentanyl consumers can cause such an effect. Looking further at month 4 (n=16; not shown), the mean TTS-fentanyl doses reached again 96.9 µg/hr, while the mean dose for the total group is 132, 5 $\pm$ 11µg/h. at month 4. Similarly, the number of patients in the subcategory aged 80 years and over was very limited (respectively 20 patients and 6 patients at months 1 and 3). In the elderly patients, the median (95% CI) TTS-fentanyl dosage at endpoint was 100 (75-100) µg/hr. as it was for the total group 100 (100-100) µg/h. The number of elderly subjects and the total group patients using rescue morphine for breakthrough pain was 61% and 55% respectively at month 1 compared to 59% and 54% respectively at endpoint.

3.2.5.6 Opioid naïve patients

TTS-fentanyl doses in the opioid naïve patients were comparable to the total Evaluable population, starting with the lowest dosage available (median (95% CI): 25 (25-50) µg/hr) to a median (95% CI) delivery rate at study endpoint of 100 (75-150) µg/hr. Less rescue morphine was used. The median (95% CI) rescue morphine dose was 10 (0-40) mg/day after one treatment month and 5 (0-50) mg/day at endpoint.

3.2.6 Tolerability data (Safety population)

3.2.6.1 Overall tolerability

Serious adverse events (death or hospitalization)

In this terminally ill patient population, the reported serious adverse events in 61.6% of the subjects (n=407) mainly included death, which never was related to the study drug in the opinion of the investigators and always related to the progression of the underlying disease. Eighteen serious adverse events other than death occurred in 15 patients, namely moderate to severe injury (n=13, falling, hemorrhage, haematoma, fractures, incised or abraded wound), moderate constipation (n=1), severe respiratory depression (n=1) and abnormal laboratory values (twice in the same patient). One case of overdosing occurred (n=1). The outcome of these adverse events was complete recovery, except for 8 cases of injury that were still present at study endpoint and one patient died of the injury.

In only in 2 of these 15 patients, the investigators indicated that the adverse events could possibly be related to the study drug. The first case concerned a 56-year-old male patient suffering from carcinoma of the tongue base who was converted from oral morphine 120 mg. daily to TTS-fentanyl 50 µg/hr. Nine days after conversion the patient developed severe respiratory depression with favorable outcome. He discontinued TTS-fentanyl therapy. The second case was a 42-year-old female patient with lung carcinoma who developed drug-related moderate constipation together with injury for which she was hospitalized. Recovery was reported and the study drug was continued. No other serious adverse events, deaths inclusive, were found related to the study drug.

The elderly patient group demonstrated a slightly but statistically not significant higher incidence of serious adverse events, 64.8% compared to 61.6% for the total patient group. This difference was completely explained by the increased number of

non-drug-related deaths in the advanced age group. Other serious adverse events in this specific patient group were injury (n=6) and the case of overdosing. In the age group of patients 70 years and older, no serious adverse event was reported, with the exception of death, probably related to the underlying disease.

Non-serious adverse events (hospitalisation not necessary)

Non-serious adverse events consisted mainly of gastro-intestinal, psychiatric and nervous system disorders: 5.1% of the patients developed nausea, 4.4% vomiting, 2% confusion, 1.8% somnolence and 1.1% headache. Frequency and severity of constipation were evaluated separately and in-depth at each monthly visit and the results are detailed in the next paragraph. In contrast to these results, constipation was rarely (0.8%) reported as an adverse event as such. Moderate dyspnoea was found in 0.8% of patients. Four patients experienced patch related adverse events (0.6%). In the elderly patients, the same type and relative frequency of adverse events was found but the overall incidence was slightly, but not statistically significantly, higher (Table 7). In these 661 patients, 13 patients (1, 9%) were confused on occasion and all of them were ≥60 years. Somnolence was present in 1, 8% (12/661) but 9 of these 12 cases were registered in the older patients (≥60y) (9/341=2, 6%) and only 3 in the younger group (<60y) (3/310= 0, 9%).

Discontinuation due to adverse events

An adverse event, other than death, was the reason for discontinuation of the study in only 27 patients (4.1%). According to the investigators 2/3 (67%) of these cases were possibly drug-related; most frequent were nausea (n=7), vomiting (n=4) and confusion (n=3). Especially a steep increase in opioid dose promotes confusion in elderly patients. Decreasing the opioid dose, change of administration route or, a rotation of opioids can solve this side effect.

Opioid naïve patients

In the opioid naïve patients in the study (n=55) no serious adverse event was registered, except for non-drug-related death in 34 patients (61.8%). Two patients discontinued the study due to an adverse event (1 subject because of vomiting and 1 subject because of headache, nausea and vomiting). The total adverse event rate was comparable to the total Safety population. None of the patients experienced respiratory depression (Table 7).

Table 7: Number of patients (%) reporting adverse events (Safety population).

	Total n=661	Elderly n=341	Opioid naïve n=55
Any adverse event	460 (69.6)	255 (74.8)	38 (69.1)
General disorders e.g. death, injury	423 (64.0)	232 (68.0)	35 (63.6)
Nervous system disorders e.g. headache, dizziness	23 (3.5)	16 (4.7)	2 (3.6)
Gastro-intestinal disorders e.g. nausea, vomiting	54 (8.2)	37 (10.9)	4 (7.3)
Psychiatric disorders e.g. confusion, somnolence	34 (5.1)	24 (7.0)	2 (3.6)
Respiratory system disorders e.g. dyspnoea, coughing	9 (1.4)	6 (1.8)	1 (1.8)
Skin & appendages disorders e.g. increased sweating, pruritus	10 (1.5)	8 (2.3)	1 (1.8)
Urinary system disorders e.g. haematuria, urinary retention	7 (1.1)	6 (1.8)	0 (0)

3.2.6.2 Constipation (Evaluable population)

Frequency and severity of constipation were assessed separately and in-depth at each monthly visit. In contrast, in the Safety population constipation was rarely (0.8%) reported as an adverse event as such. Therefore, constipation is discussed in relation to the Evaluable population, in which approximately 40% of patients with available data, reported mild to severe constipation at the monthly visits. This frequency remained relatively constant over the study period. The severity of constipation was also similar at the month 1 visit compared to study endpoint and not influenced by age (Table 8).

Table 8: Number of patients (%) according to severity of constipation (Evaluable population)

	Total		Elderly	
	Month 1	Endpoint	Month 1	Endpoint
No constipation	229 (59)	237 (58)	120 (58)	117 (54)
Mild constipation	75 (19)	80 (20)	40 (19)	46 (21)
Moderate constipation	62 (16)	69 (17)	35 (17)	41 (19)
Severe constipation	22 (6)	23 (6)	11 (5)	12 (6)

Only 6% of patients suffered from severe constipation at month 1 and at endpoint. In the other constipated patients, this was mild to moderate. There were no differences regarding the occurrence and mild or moderate constipation (incidence is for all between 16 and 21%) between the total population of evaluable patients and the elderly patients.

Since patients included in this study associated both TTS-fentanyl therapy and oral morphine rescue medication, the occurrence of constipation could not directly be related to one of the drugs. More information about possible causal relationships could therefore be obtained by regrouping the patients to the respective applied

posologies. TTS-Fentanyl doses of 25-50 µg/hr were considered as "low dosages"; all doses of 75 µg/hr. and above were called "high doses". The rescue morphine doses were classified in "low" (0-40 mg daily) and "high" doses (above 40mg daily). Table 9 shows the percentages of patients that reported constipation at month 1 and at study endpoint for these subgroups.

The total group:

At month 1, the frequency of constipated patients with low dose morphine was respectively 36% (low dose fentanyl) and 37% (high dose fentanyl) and these figures did increase, but not statistically significantly (p= 0.062 Fisher's Exact Test), by increasing the morphine dose (50% and 47%). If at month 1 the fentanyl dose increased, the frequency of constipation remained stable at 37% for low morphine dose and at 47% for high dose morphine (p= 0.58).

At endpoint, the frequency of constipated patients with low dose morphine was respectively for low and high dose fentanyl 38 and 35%, but increased significantly (p= 0.0007) with increasing doses of morphine to 47% and 57% for low and high dose fentanyl. Increasing the fentanyl dose at endpoint did statistically (p=0.64) not increase the constipation frequency for low (38 tot 35%) or high (47 tot 57%) dose morphine using patients.

The elderly group:

At month 1, the frequency of constipated patients with low dose morphine was 42% under low dose fentanyl and 32% under high dose fentanyl and these figures did increase, not statistically significantly (p = 0.085), to 60 and 50% by increasing the morphine dose. If at month 1 the fentanyl dose increased, the frequency of constipation even decreased from 42 to 32% for low dose morphine and from 60% to 50% for high dose morphine (statistically not significant p=0.458).

At endpoint, the frequency of constipated patients with low dose morphine was 40 and 38% for low and high dose fentanyl respectively. It increased statistically

significantly (p=0.0006) with increasing dose morphine to 63% and 67% respectively for low and high dose fentanyl. Increasing the fentanyl dose at endpoint did not statistically (p = 0.64) change the constipation frequency for low (40 tot 38%) or high dose morphine using patients (63 tot 67%).

Table 9: Effect of opioid dose on constipation at month 1 and study endpoint (Evaluable population and the subgroup of elderly). Percentages of patients with constipation are presented according to the morphine dose (Low: 0-40 mg/day; High: > 40 mg/day) and TTS-fentanyl dose (Low: 25-50 µg/hr, High: ≥75 µg/hr).

Evaluable population	TTS-fentanyl Low dose		TTS-fentanyl High dose		**Elderly patients**	TTS-fentanyl Low dose		TTS-fentanyl High dose	
	M1	End	M1	End		M1	End	M1	End
Morphine Low dose	36	38	37	35	Morphine Low dose	42	40	32	38
Morphine High dose	50	47	47	57	Morphine High dose	60	63	50	67

Elderly patients taking high doses of rescue morphine were even more prone to constipation (in 3 of the 4 subgroups over 60% of patients) than the whole Evaluable population.

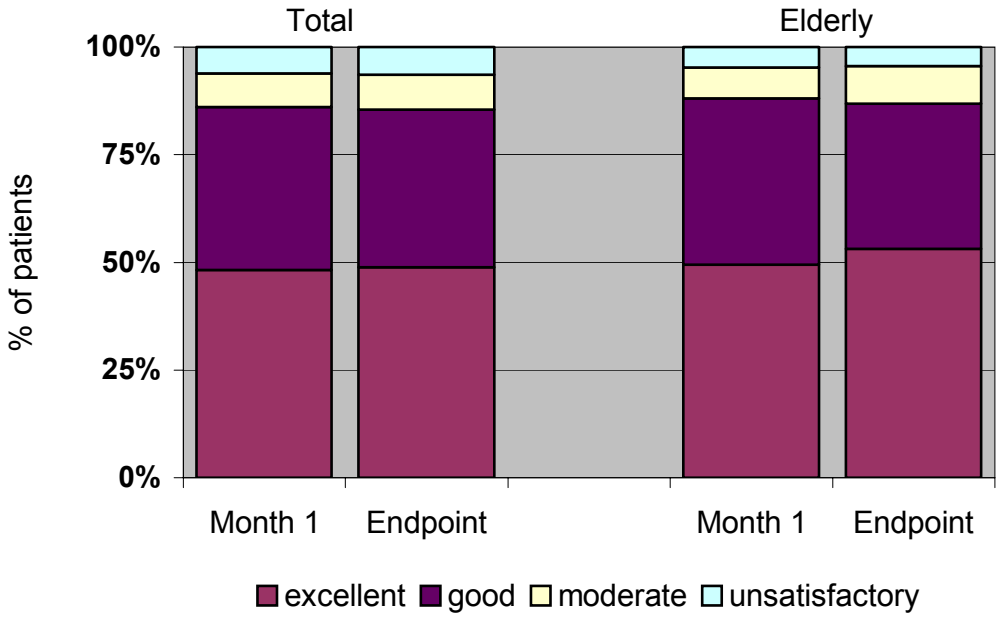
The prescription of concomitant laxatives was not restricted throughout the study period. After 1 month, 60% of the total Evaluable population and 65% of the group of elderly patients were taking laxatives. The use of laxatives further remained rather constant, in accordance with the frequency of constipation that also showed

little variation during the study period. Osmotic laxatives were the first choice for treatment, if necessary were natriumpicosulphate drops added, and further on an as needed basis a clysma could be given.

3.2.7 Appreciation of the TTS-fentanyl patches (Evaluable population)

Patients evaluated the ease of use of the patches on a 4-point scale: excellent –good – moderate – unsatisfactory (Figure 7). It appeared that more than 85% of the Evaluable population rated the convenience of the patches as "good to excellent". After 1 treatment month and at study endpoint similar scores were found. Only 6% of patients were not satisfied. The opinion of the elderly subjects about the convenience of the patches was comparable.

Figure 7: Percentage of patients in the Evaluable population and the elderly subgroup considering the ease of use of the patches excellent, good, moderate or unsatisfactory at month 1 and endpoint.



3.3 Discussion

This large open-label study in real daily clinical practice confirms the good tolerability and convenience of long-term TTS-fentanyl use in cancer patients (80-83). In contrast to classical clinical trials, this compassionate use program copes with an important inter-individual heterogeneity related to varying treatment durations, a wide range of TTS-fentanyl doses, differently progressing underlying diseases and different age populations.

3.3.1 Study discontinuation

At the moment this study was performed, TTS-fentanyl was new in Belgium and therefore its compassionate use probably often was reserved for terminally ill patients. A total of 61% of patients did not complete the planned 3-month study period because of death that in none of the cases was drug-related but mainly caused by progression of the underlying disease. This indicates that investigators' prognosis at inclusion overestimated real survival time in a large number of patients.
Insufficient pain relief led to treatment discontinuation of 17% of these cancer patients with poor life expectancy. They were further treated with systemic or epidural /intrathecal morphine administration.

The third reason for study termination was the occurrence of an adverse event (not resulting in death), most frequently nausea, vomiting and confusion. Only 4.1% of patients withdrew from the study for adverse events, including 1.4 % non-drug-related cases in the opinion of the investigator.

3.3.2 Tolerability

Typical morphine-like side effects occur with TTS-fentanyl as with other strong opioids e.g. constipation, nausea, vomiting, somnolence and confusion. However, side effects and particularly constipation and sedation have been reported to occur less frequently with TTS-fentanyl compared to sustained-release oral morphine (84,85). In a compilation of TTS-fentanyl clinical trial data, nausea, vomiting, somnolence and confusion were previously reported to each occur in more than 10% of patients (86). The current open-label study illustrates a less than 10% frequency of adverse events in this compassionate use program. This is probably attributable to a lower reporting rate, particularly in these terminally ill patients, in whom it not always is clear whether the disease or the treatment induced adverse events. One patient developed respiratory depression with favourable outcome but was withdrawn from the study. No other drug-related serious adverse events were reported, except for one patient who was hospitalized for injury and simultaneously suffered from drug-related moderate constipation. Skin tolerance to TTS-fentanyl was good; patch-related skin side effects occurred in only 0.6% of patients. Gastro-intestinal disorders and psychiatric disorders were less frequent in this data series compared to other reports (80, 82, 87 and 88). Although it is generally accepted that patients with an increased risk for constipation should receive prophylaxis (89), the co-prescription of laxatives was relatively low in this open study (60% of patients and 65% of elderly patients were using laxatives).

The fact that morphine was used as rescue medication in addition to TTS-fentanyl complicates the interpretation of side effects that might have been caused by either treatment regimens. This particularly applies to the interpretation of the constipation data. Interesting results were obtained comparing dose-relationships of morphine and TTS-fentanyl with respect to constipation. At least at a low dose of morphine, the rate of constipation was not found to be TTS-fentanyl dose related, even in the elderly (32 to 42%). In contrast, constipation was clearly more frequent (47 to 57%) in the patients using high doses of rescue morphine and particularly in elderly

patients (63 to 67% at endpoint). This is in line with data from clinical trials reporting that constipation occurred less frequently following TTS-fentanyl than with morphine administration (84).

3.3.3 TTS-fentanyl treatment in different populations

Whatever the population studied, a wide range of TTS-fentanyl dosages (max. 950 µg/hr.) were used over different, sometimes long, periods of time (up to 2½ years). The appropriate initial TTS-fentanyl doses were derived from the existing opioid treatment during the stabilization phase. It has previously been estimated that the recommended dose-equivalent tables (conversion ratio 150:1) are very conservative (81, 89, and 90). The broad safety margin leads to a large proportion of opioid tolerant patients, namely those taking opioid doses equivalent to oral morphine up to 134 mg/day, all being converted to the lowest available TTS-fentanyl dose. This leads to frequent initial dose increments and might translate into initial TTS-fentanyl under dosage, with patients dropping-out early due to insufficient response. Therefore, Breitbart et al. have recently proposed a more aggressive dose-equivalence scheme (ratio 100:1) (90).

TTS-fentanyl dose increments were most frequently found at the beginning of the study and stabilized by month 2. This probably reflects that patients with the fastest disease progression dropped out early. It also suggests that the recommended dose equivalence tables (150:1) are conservative, as mentioned in the preceding paragraph.

Time courses of the frequency of rescue morphine use and TTS-fentanyl dose increases were superimposed showing that the guideline to replace all breakthrough morphine exceeding 60 mg/day by an equivalent dose of TTS-fentanyl 25µg/hr. was followed in an excellent way by the investigators. Dose decreases were rare,

which reflects that the risk of prescribing overdoses of TTS-fentanyl is relatively low in patients where anti-tumor treatment no longer is possible.

The total group of elderly patients of 60 years and over could not be differentiated from the whole patient group, neither with respect to dosage scheme nor to tolerability, except for a slight increase of non-serious adverse events. However, 'within' the group of elderly patients, consumption of TTS-fentanyl decreased with increasing age and was lowest in the category of patients of 80 years and over. Although sample sizes were limited in these age subcategories, this indicates perhaps that very old patients communicate pain less well or that investigators are more prudent in prescribing opioids. Overall, our results confirm previous findings of Jakobsson (91) who demonstrated that it is possible to obtain safe pain control with TTS-fentanyl in terminally ill patients, irrespective of age.

A total of 55 completely opioid naïve patients entered the study and started TTS-fentanyl therapy directly, omitting WHO step 2 of the analgesic ladder. Compared to their opioid non-naïve colleagues, these patients were characterized by longer treatment duration probably because they were in an earlier phase of their cancer stage with less painful lesions. With regard to the median TTS-fentanyl start and endpoint doses, the opioid naïve population could not be differentiated from the total population, but a lower need for rescue morphine was found. The tolerability was similar to that in the strong opioid tolerant patients, with none of these patients developing respiratory depression. It appears that starting directly with appropriate TTS-fentanyl was well tolerated in this group of opioid naïve patients. A similar experience in a small study of 28 patients has been reported by Vielvoye-Kerkmeer (92).

3.3.4 Acceptability of the patches

Corresponding to previous reports, patient acceptance of the transdermal application was high (84, 87). The ease of use of the patches, that sometimes have been claimed to be less suitable for elderly patients (91), obtained the same level of appreciation from the older patients. Approximately 85% of patients rated the convenience good to excellent. It was surprising that more than half of the subjects, who left the study due to insufficient pain relief, were nevertheless satisfied with the use of the patches.

3.4 Conclusion:

From the analysis of this large experience we conclude that, despite great inter-individual variability in treatment duration and dosage, TTS-fentanyl application every 3 days for the treatment of cancer pain is well tolerated and well accepted by most patients, including the elderly and opioid naive, at comparable dose regimens.

Chapter IV:

Opioid tolerance:

A self limiting phenomenon

4.1 Patients and Methods

4.1.1 Study design

Chapter IV studies the long-term survivors described in Chapter III.

4.1.2 Statistics

Descriptive statistics were performed regarding the monthly assessments. The TTS-fentanyl consumption data were normally divided in the first 12 months of follow-up but were asymmetrically divided for the last 12 months, caused by the much smaller number of patients and the greater variability in fentanyl doses. Because the number of patients was much larger during the first year compared to the second year, the means $\pm$ standard deviations were measured. The combination of symmetrical and asymmetrical data in one plot is known in statistics as the phenomenon of heteroscedasticity. Therefore, data corrections have to be performed for constructing linear regression curves. The initial mean fentanyl doses have to weigh more than the later doses. This is done by multiplying all mean doses with $1/\sqrt{SD}$. In all the plots, there is an increase in mean fentanyl doses during the first 4 months, followed by relatively stable doses during the following months, except for 2 periods of 3 months in the patients $\geq$60 years. For this reason, a linear regression curve is constructed for the first 4 months and a second one for the remaining months. Statistical calculations for constipation frequency, constipation intensity and the use of laxatives were only done if at least 10 patients per evaluation point were available.

4.2 Results

4.2.1 Subjects

Forty-five Belgian investigators recruited between June 1994 and 1997 a total of 663 palliative cancer patients with a wide range of no longer treatable or

primarily untreatable malignancies and suffering from moderate to severe cancer pain. Data are available from 661 patients with at least 1 TTS-fentanyl application. Only 412 (62%) and 210 (32%) patients survived after respectively 1 and 2 months and 171 patients (25.8%) survived after a treatment period of over 13 weeks. Figure 8 shows the number of patients of whom data of drug doses and adverse affects are available at the respective follow-up times. About 75% of the patients died due to tumour progression in the first 3 months after the start of the TTS-fentanyl treatment. At the follow-up after 4 months only 162 patients (24%) survived.

Figure 8: The total number of patients available at each evaluation point in function of time (in months: 1= baseline, 2-25 are the numbers for months 1-24).

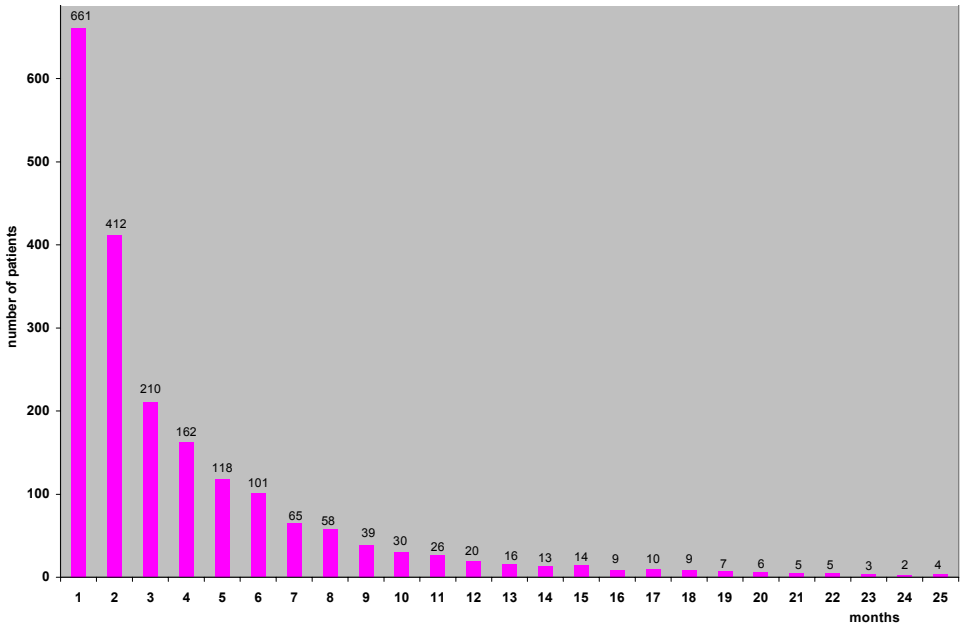
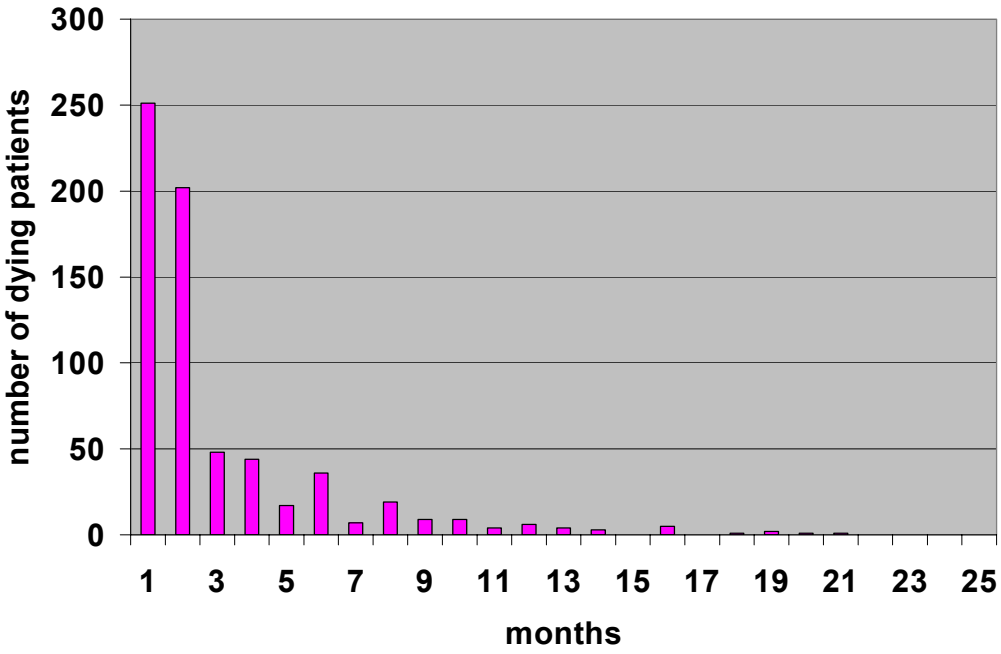


Figure 9 illustrates clearly that there is a breakpoint during the third - fourth month in the histogram that represents the numbers of deaths per month. The number is sharply decreasing in the first 3 months and comes further down smoothly in the second part. The possible impact of opioid tolerance was analysed in the patients who survived more than 13 weeks (n = 171) patients. Thanks to their favourable

survival were these cancer patients ideal candidates to study long-term cancer pain treatment with strong opioids.

Figure 9: Number of deaths per monthly interval in function of time.



4.2.2 Demographics and baseline characteristics

Both genders were equally distributed over the study population and the tumor type was known for all 169/171 patients: gastro-intestinal 26.4%, breast 25.6%, lung 8.3%, prostate 6.6% and other 33%. The age groups of <60 years and ≥60 years contained respectively 91 (53%) and 80 (47%) patients.

4.2.3 Fentanyl doses

Figure 10 gives the mean fentanyl doses $\pm$ SD (µg/h.) for the 171 patients (surviving more than 13 weeks) from study entry until death. During the first 4

months there is a progressive monthly increase from 46 to 135µg/h. Between 5 and 10 months the doses remained stable between 100 and 150 µg/h. After 10 months, the range became somewhat greater and the data were confined between 50 and 215 µg/h. Linear regression curves were constructed with F=27.48 in the first 4 months. This high F-value indicates that the slope of the curve is steep. The very low P-value of 0.0135 indicates that there is a highly significant relation between the mean values and time. The second part of the linear regression curve is decreasing smoothly as is indicated by the low F-value of 3.68. This second part has only a P-value of 0.71(not significant).

The initial steep slope (F= 32.16) is also seen for the patients <60 years with also a statistical significant probability (P=0.0109), followed after month 5 by a very smooth linear curve with a F-value of 0.86 and a P-value of 0.3665 (not significant) (Figure 11).

For the patients ≥60 years, the initial slope is a little bit less steep (F= 14.06) but again with a highly significant P-value of 0.0331. The second part of this linear regression curve has a larger spread of data (P= 0.0625) due to the wider range of the mean doses from 30 to 262 µg/h. The second part of the linear curve has a smooth slope with F = 3,94 (Figure 12).

During the first 4 months the mean opioid doses progressively increase over time in the 3 curves (Fig. 10-12). The regression curves fit the data very well with R^2 values of 0.9016 for all patients, and 0.9147 and 0.8242 for respectively the patients up to 60 years and those from 60 year and over. There is for these months in the 3 curves a significant correlation between the mean doses in function of time (P <0.035 for the 3 curves).

After 4 months the regression curves are negative in all three figures (Figure 10-12) and the respective R^2 values were respectively 0.1696 (for all patients), 0.0482 (for <60 years) and 0.1798 (for ≥60 years patients) which reflects that the linear curve does not perfectly fit the data due to the wider range of doses. Here significance between dose and time was absent (P >0.05).

Figure 10: Mean TTS-fentanyl doses ± SD (µg/h.) in function of time (months) for all patients. Number of patients and linear regression curves with F- and P-values are shown.

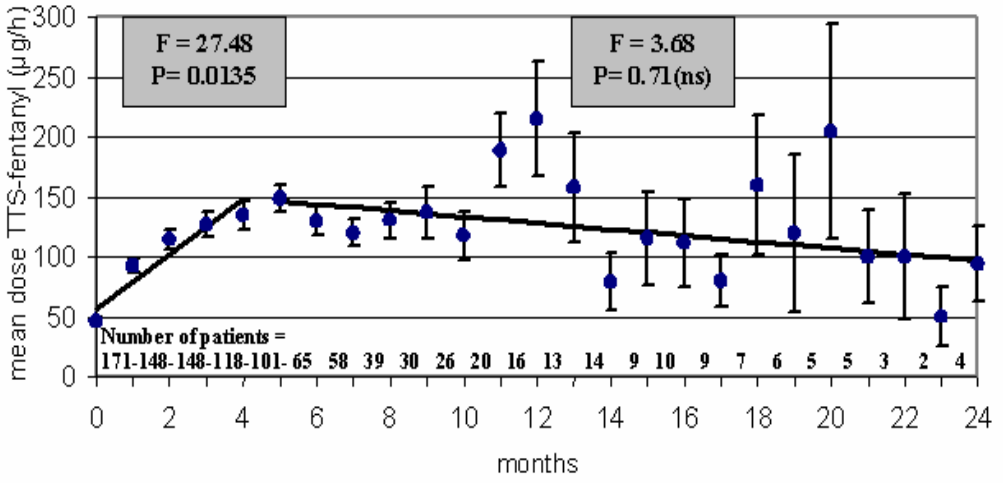


Figure 11: Mean TTS-fentanyl doses ± SD (µg/h.) in function of time (months) for patients <60 years. Number of patients and linear regression curves with F- and P-values are shown.

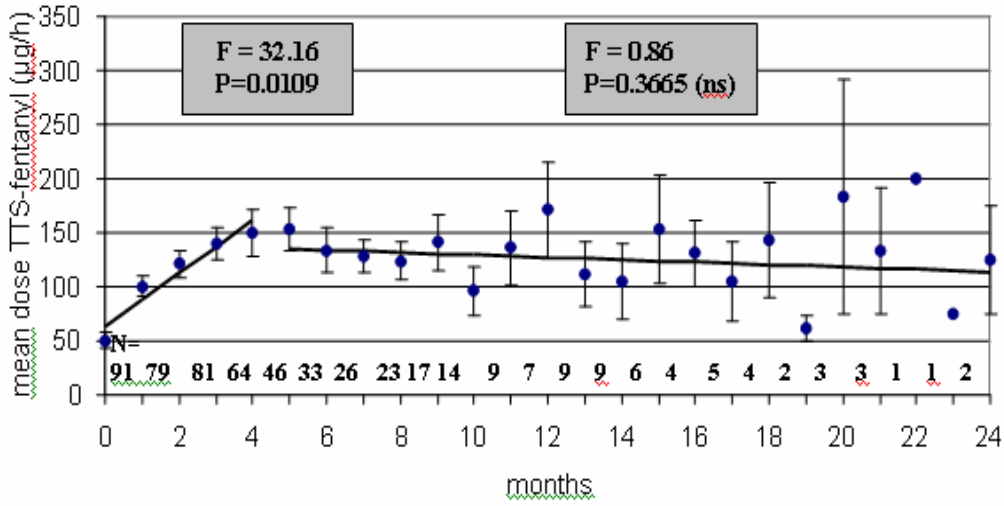
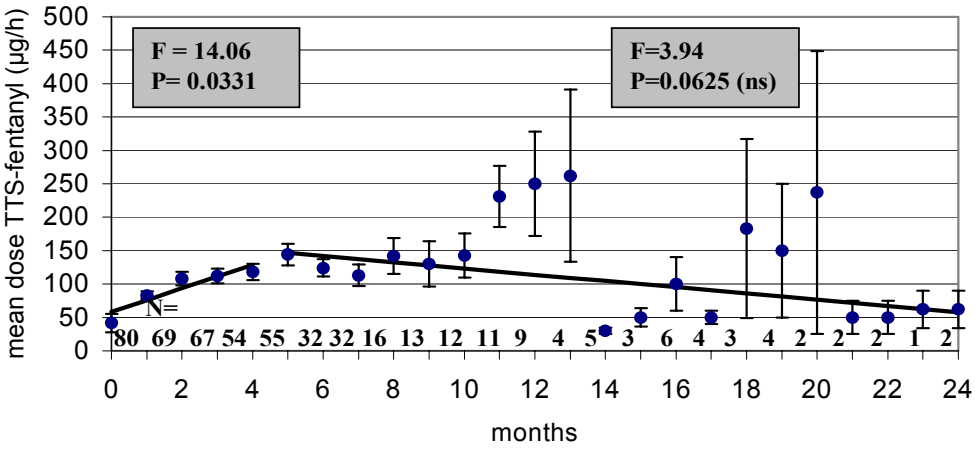


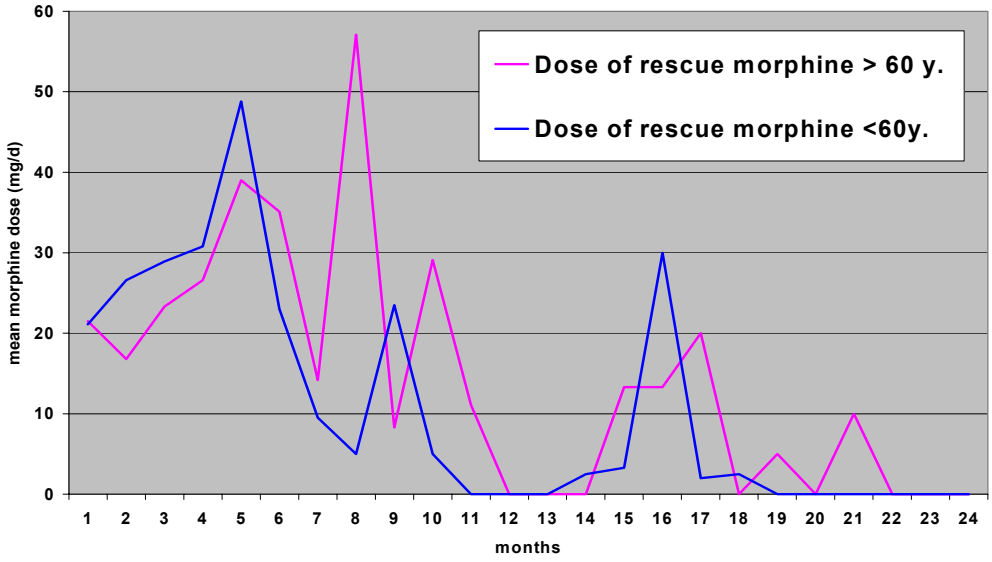
Figure 12: Mean TTS-fentanyl doses ±SD (µg/h.) in function of time (months) for patients ≥60 years. Number of evaluated patients per month is represented. Linear regression curves with F- and P-values are shown.



4.2.4 Rescue Morphine doses

The mean rescue morphine dose varied between 0 and 57 mg/d. and never exceeded 60 mg/d., in accordance with the prescriptions of the study protocol. The protocol indeed specified that if the rescue morphine dose to keep the pain score below 3.5 on a 10-point visual analog scale was 60 mg/d. or higher, then the next TTS-fentanyl application was incremented with 25µg/hr. There was no statistical difference in rescue morphine dose within the two age groups and the doses decreased slowly during the study; during the second year there was not much use of rescue morphine medication (Figure 13). This decrease in the use of rescue medication started after 6 months for the younger and after 8 months for the elderly patients.

Figure 13: Mean doses of rescue morphine in mg/d for patients < and ≥60years in function of time.



4.2.5 Pain relief

The mean pain scores were effectively below 3.5 on the 10-point visual analog scale. Insufficient pain relief led to TTS-fentanyl treatment discontinuation in 17% of the patients and these patients were further treated to the discretion of the treating physician. They have mainly chosen for intravenously morphine and continuous spinal infusions administration.

4.2.6 Side effects

Constipation was absent in 63-88% of all checks in patients <60 years and in 54 – 77.8% of checks in the patients ≥60 years (Table 10). Less than 26% of the young patients experienced mild to moderate constipation and only 0-7.2 % had sometimes severe constipation. In the older group mild and moderate constipation were slightly more frequent (from 7.7 to 46%) and less than 5% of these elderly patients developed severe constipation (Table 10). The constipation

never obliged the treating physician to stop the opioids or prevented the investigator to increase the dose of the strong opioids according to the pain intensity.

Table 10: Different severity of constipation for patients <60 en ≥60 years during long term use of TTS-fentanyl and morphine for breakthrough or incidental pain.

	No constipation	Mild constipation	Moderate constipation	Severe constipation
<60 years	63-88%	5-26%	0-14%	0-7.2%
≥60 years	47-77.8%	12-46%	7.7-25%	0-4.7%

No constipation was more frequent registered in the younger than in the elderly patients (Figure 14).

Figure 14: Percentage of patients (< and ≥60years) without constipation in function of time (months) with a least 10 available patients per point.

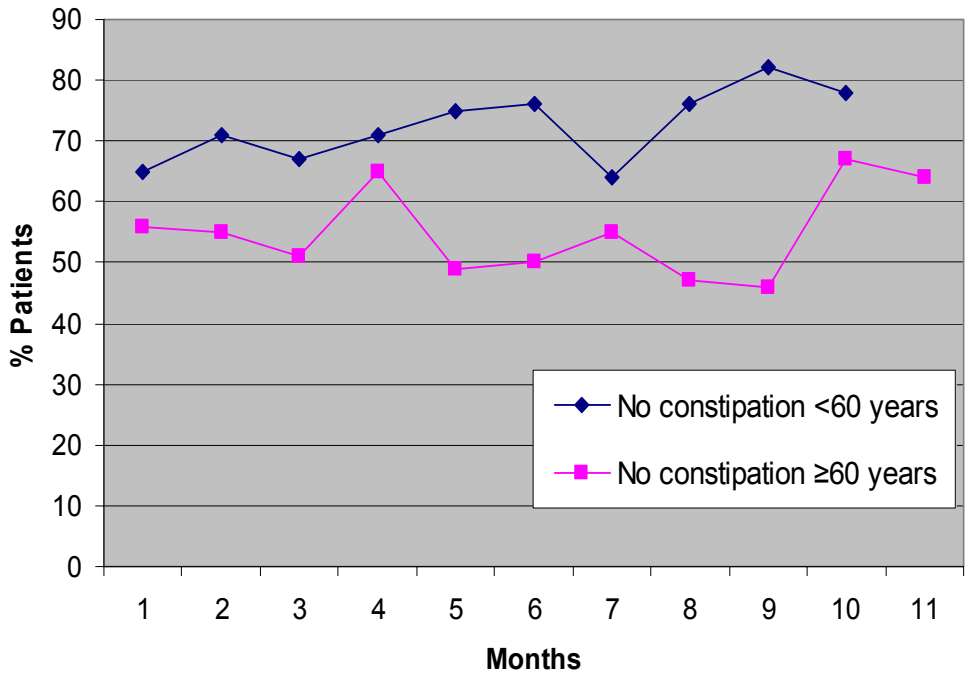


Figure 15: Percentage of patients (< and ≥60years) with different severity of constipation in function of time with a least 10 available patients per point.

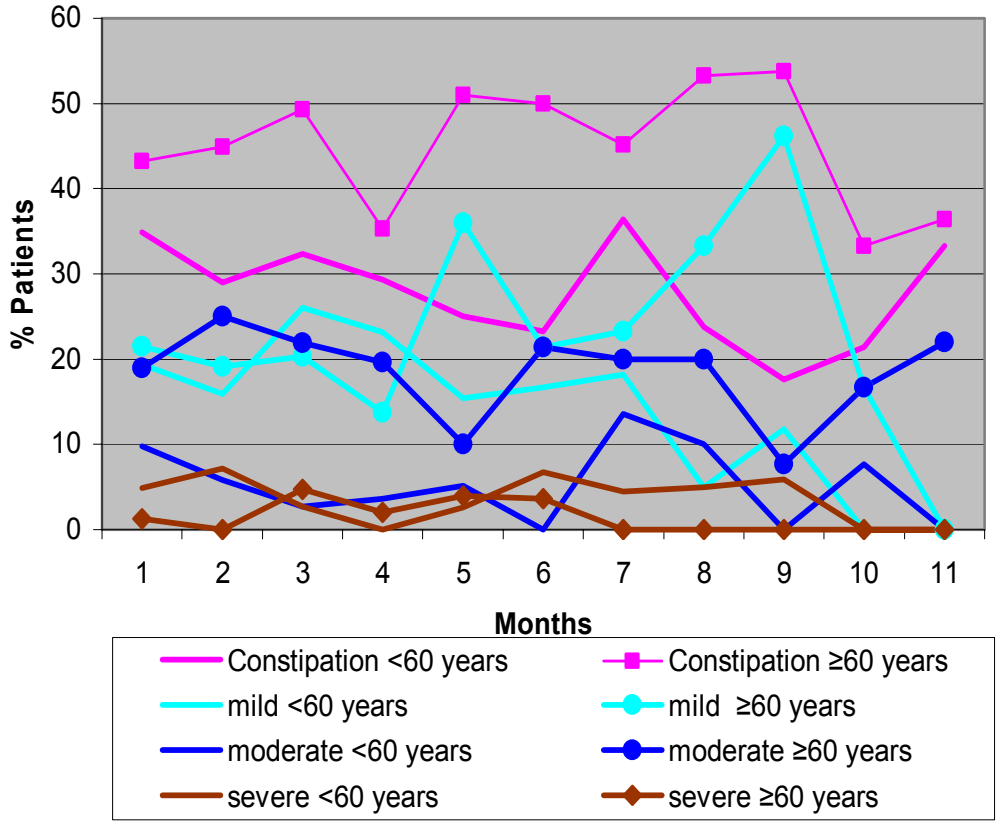


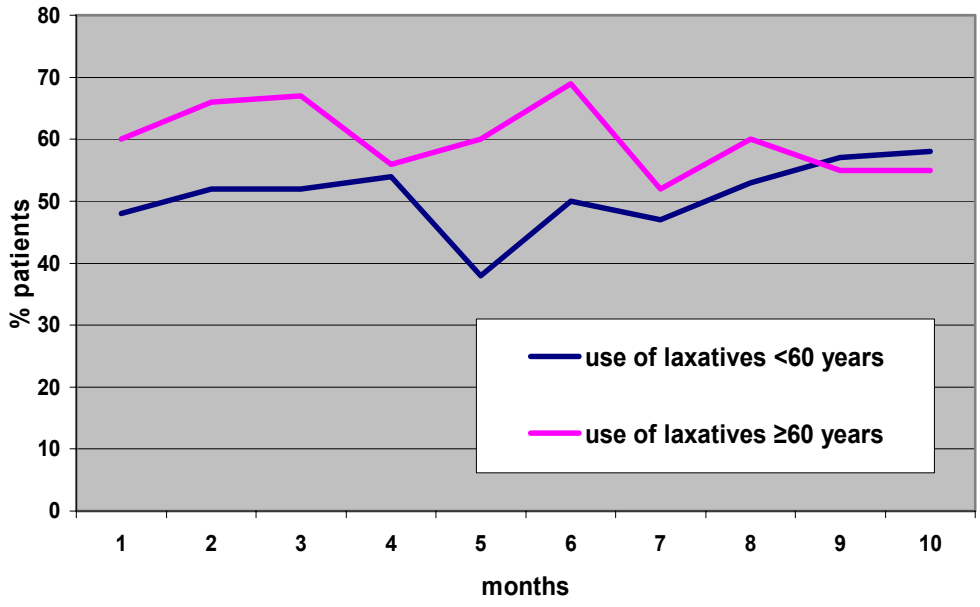
Table 11: Linear regression curve fitting and statistical analysis of different severity of constipation in patients < and ≥ 60 years from Figure 15.

	R^2	Parameter estimate	P
All constipation	0.669	-17.2	<0.0001
Mild constipation	0.260	-9.99	0.0277
Moderate constipation	0.656	-12,3	<0.0001
Severe constipation	0.311	2.65	0.0205

In table 11 is the statistical analysis summarized from the data in Figure 15. The total group of young patients has 17.2% less constipation than the older patients, which is statistically significant ($p<0.0001$). The high R^2 mentions that the data fit well on a linear regression curve. The younger patients have 12.3% less moderate constipation and this also is highly statistically significant ($p<0.0001$). For the patients with mild and severe constipation do the data fit less well (low R^2) although there is still statistically significance with 9.99% less mild constipation in the younger group. Younger patients have 2.65% more severe constipation ($P=0.02$).

The percentage of patients under and above 60 years using laxatives was not different over 12 months (Figure 16). The younger patients used not significantly less frequently laxatives (m = 38$\pm$7% of the checks) than the elderly patients (m = 46 $\pm$11% of the checks).

Figure 16: Percentage of patients (< 60 and ≥60 years) using laxatives in function of time.



4.3 Discussion

Many patients, families, nurses and physicians harbour reluctance and fears towards opioid tolerance. This misconception is frequently used to justify the postponement of effective cancer pain treatment with opioids as long as possible, "to reserve this effective pain treatment for the more difficult terminal phase of life". In the meantime however many patients worldwide suffer from easily treatable cancer pain. A life expectancy of more than three months was one of the eligibility criteria for this open label multicenter TTS-fentanyl study. However within 3 months already 75.6% patients had died! Figure 8 demonstrates that only 24.4 % of cancer patients without antitumoral treatment survive more than 3 months. The data strongly support to implement effective cancer pain treatment when there is pain. The last phase of life is already present in most of those patients, a fact of which many caregivers are not fully aware. These data give raise to the hypothesis that real life expectancy in advanced cancer patients is substantially overestimated sometimes by caregivers.

Figure 9 suggests that cancer patients dying within or after 13 weeks of follow-up constitute two groups with a totally different clinical course. The first group consists mainly of patients with fast growing tumours resulting in a short survival time while the second group harbours slowly progressing tumours with reasonable lifetime left before dying. Most published data and statements about opioid tolerance are based on the analysis of opioid consumption in cancer patients belonging to the first rapidly dying group. Many other factors than opioid tolerance can influence the opioid consumption in this terminal phase of life: disturbed gastro-intestinal absorption, changed drug metabolism and excretion, interaction with other drugs, anxiety, changed pain threshold, sleep disorders, loss of social function, fear of the dying process.

Moreover, many statements about opioid tolerance are vague, anecdotal or lack solid scientific ground. Some of these statements: "Increases in daily morphine

dose in palliative cancer patients, when they occurred, generally developed over weeks to months, and a pattern of rapid escalation in morphine dose did not occur in the 17 patients treated over a mean time of 32 days" (71). The "larger" studies about "long term" strong opioid consumption assessments consider mean treatment periods of 158 days in 51 patients (72). It is impossible to assess from such data how important or unimportant the phenomenon of opioid tolerance really is in the treatment of cancer pain. Better data are not available in literature (93, 94).

In an attempt to start clarifying this important scientific and clinical problem of opioid tolerance, we analysed the opioid consumption data of 171 patients who survived at least 13 weeks. This is a very large number of far advanced, but very slowly progressing, cancer patients. No oncological treatment interfered with the pain treatment and the long follow-up time (24 months) with very few deaths per month minimises the possible influence of all the "end-of life factors" that could interfere with opioid tolerance or opioid dose modifications.

Figure 10 demonstrates that, after an initial steep slope during 4 months, there is a relatively stable opioid consumption for up to 24 months after starting TTS-fentanyl. Also for the mean TTS-fentanyl doses in the age groups <60 years and ≥60 years (Figure 11 and 12) a progressive increase is noted in the first 3- 4 months. Especially the curve for the younger patients is more flat from month 4 until 2 years follow-up. The range in fentanyl doses in the elderly population becomes wider after month 10. The explanation for this is not evident. Is there a less accurate reporting of pain in some elderly with subsequent under dosages, or is it caused by the more difficult or even sometimes no longer existing communication with elderly persons and subsequently relative over dosages to avoid non expressed pain?

In figures 10-12 do the linear regression curves fit well with the data during the first 4 months ($p<0.05$ and high R^2) while this is less the case for the second part of the curves due to the larger standard deviations in opioid doses.

The amount of strong opioid doses given in these palliative advanced cancer patients is common in clinical practice and fits well with the literature. Donner et al. started with mean TTS-fentanyl doses of 69.5 µg/h. and ended up with 167.7µg/h after a mean treatment period of 158 days (80). In the study of Slaon et al. the mean starting dose was 135 mg morphine/day (~TTS fentanyl 50µg/h) and 244 mg morphine per day (~TTS fentanyl 75 µg/h) at study completion after only 32 days (95).

The results of this study concerning a large number of patients over 2 years offer scientific evidence that opioid tolerance can easily be overcome during prolonged pharmacological cancer pain treatment. The hypothesis that tolerance plays an important role and that a progressive increase of opioid doses is inevitable to maintain an acceptable level of pain relief is invalidated. Attention has to be given to the positive linear regression lines of the mean opioid dose/time curves during the first four months (Fig. 10-12). These lines fit very well the mean opioid doses, reflected by their high R^2 values, all above 0.82.
There is a clear increase in fentanyl doses in time which is most likely caused by opioid tolerance in these patients with very slowly progressing tumours. There is no evidence that in untreated advanced cancer patients initial fast tumour growth would slow down or stop spontaneously after 3 or 4 months. The opioid tolerance enhances the mean daily dose of opioids during the first 4 months with 100 to 200 %. This tolerance effect seems to be limited in quantity but also in time. The linear regression lines after month 4 become even negative (Figure 10-12) with very low R^2 values between 0.1696, 0.0482 and 0.1798 for respectively all patients, the <60 and ≥60 year old patients. This indicates that there no longer is a positive relation between opioid dose and time. These negative

regression lines do not indicate that the opioid doses in individual patients were decreasing, since in reality the most far advanced cancer patients, mostly the high dose opioid consumers, die first during the follow-up time and can cause this decrease in mean overall opioid consumption. Patients with a slightly better prognosis survived for a longer time. They were low opioid dose consumers what is reflected in these negative linear regression curves after month 5.

Decreasing mean opioid doses during follow-up could also be the result of the drop-out of patients for reasons of insufficient pain relief or intolerable side effects. Both issues would however happen very early in the treatment and would influence the mean opioid dose during the first 4 months.

In function of time there was neither an increase of constipation frequency, nor constipation severity, nor an increased use of laxatives. Long term use of strong opioids seems to be well tolerated by both young and older patients.

4.4 Conclusion

This study with many patients (n=171) and very long follow-up time (24 months) offers evidence that opioid tolerance exists and really has an effect on the strong opioid doses in cancer pain therapy. Opioid tolerance can be responsible for the progressive increase of the mean strong opioid dose by 100 to 200% during the first 3-4 months of cancer pain treatment. After month 4, there is no further mean opioid dose increase shown in this study. Opioid tolerance seems to be a process that is limited in dose and in time. There is no reason to hypothesise that tolerance will modify the opioid doses again during follow-up times after more than 2 years, a follow-up period which is irrelevant in this clinical situation of advanced cancer patients but is relevant for patients with chronic benign diseases and pain.

Constipation is a rare but manageable side effect and therefore can this never be a reason to withhold cancer patients an effective pain therapy.

We conclude that effective pain treatment with strong opioid dosing according to the WHO guidelines in relation to the pain intensity is an effective and safe procedure. Opioid tolerance exists clinically but seems to be a process of limited importance that causes a dose enhancement of 100 to 200% that is only be seen during the first 3-4 months of opioid treatment.

Chapter V:

Palliative sedation for refractory symptoms in terminal palliative cancer patients:

Procedure and results in UH Leuven

5.1 Definitions

Many publications, most of them retrospective, describe sedation used as one of the comfort measures in palliative patients applied in a few up to more than 50% of dying patients. “Light” sedation given to control patients with some degree of delirium, anxiety or insomnia is not the subject of this analysis because this does not constitute an ethical problem. The consciousness of these patients is only slightly modified to help them to continue to live more comfortably. Withholding this light sedation is withholding good clinical practice and has to be evaluated as unethical. But the definitions of sedation are vague, even the terms of terminal and controlled sedation are not well defined and could be interpreted differently. Terminal sedation is widely used in the literature but should be avoided because it could be interpreted as “sedation with the intention to terminate the patient’s life”, and is therefore a misleading term. ‘Controlled sedation’ suggests that the sedation be used to control everything, with a tendency to palliative persistency. Therefore it is probably better to speak about ‘palliative sedation’ to indicate that the sedation is used to palliate a refractory symptom in a patient’s last phase of life. Palliative sedation becomes gradually the most used term for the treatment of refractory symptoms in terminal palliative patients. We’ll reserve this term in this study for those situations where the terminal palliative patient and his physician intend to obtain a deep sleep. The sedation is done without hastening or causing death, just to relieve suffering from one or more intractable symptoms, when all other interventions have failed and the patient is perceived to be close to death. The patient can no longer communicate during this sedation and this constitutes an intrinsic ethical problem. Many people perceive it as a great difficulty to differentiate palliative sedation from (slow) euthanasia.

In many papers the indications for sedation are not well defined and the practical procedures are mostly not reported. Clinical research is necessary to investigate

the indications and the effectiveness, and to elucidate the possible role of palliative sedation in terminal patients.
This study will analyse the indications, the procedure and efficacy of palliative sedation for refractory symptoms in terminal palliative cancer patients in the University Hospitals of Leuven. Our own data will be compared with the literature.

5.2 Patients and methods

Palliative terminal cancer patients in the UH of Leuven are informed since 1997 by the palliative support team that they don't have to suffer in the terminal phase of life. They have the opportunity to ask for palliative sedation to relieve intractable pain or other unbearable symptoms if they remain unresponsive to all other interdisciplinary palliative measures.
From 1997 to 2002 we prospectively registered 26 palliative terminal cancer patients suffering from one or more refractory symptoms in which any form of oncological or palliative treatment no longer was meaningful and standard palliative care had failed to control the symptoms.

The first ten patients (1997 until September 1999) were in-hospital patients for whom the mobile hospital-based palliative support team (PST) was consulted. The next 16 patients (September 1999 until December 2002) were patients in the palliative care unit (PCU) of the hospital. All patients were fully conscious and requested themselves to start palliative sedation because they could no longer bear the pain or the suffering and were not able to pass the last phase of their life comfortably and with dignity.

Midazolam was always used to sedate these patients. It is a benzodiazepine with a fast on- and offset, it is water soluble and can be given intravenously, subcutaneously and intramuscularly. Midazolam was mostly started in a small

bolus (7.5-15 mg S.C.), to induce sedation, concomitant with the start of a continuous subcutaneous infusion. The continuous dose rate was assessed by the clinician based on the personal medical history of the patient, the individual patient's experience with benzodiazepines and the intensity of the refractory symptom(s). The midazolam dose rate was titrated so many times a day as was necessary to control the intractable symptoms until death.
With the start of sedation, a close medical follow-up of the patient and support for the family and the caring team were initiated to help them to cope with this exceptional situation.

Midazolam is the drug of choice to sedate. Because of its rapid on- and offset is it an excellent sedative to continuously optimise the dose in function of the symptoms and especially to manage intermittently sedated patients.

5.3 Results

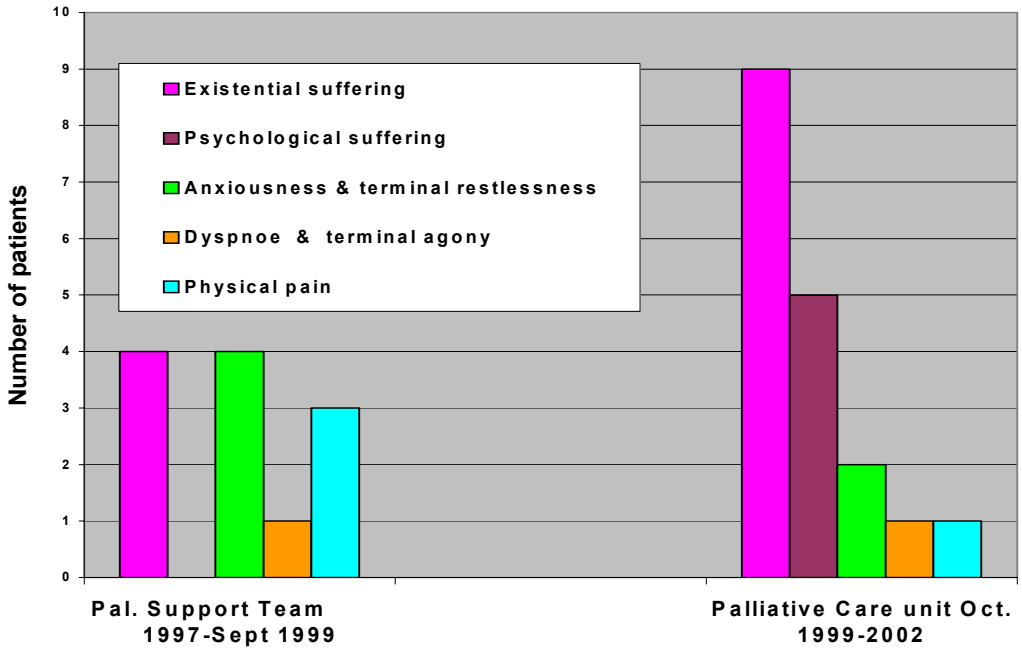
The prevalence of refractory symptoms (Figure 17), the demographics of all patients, the doses of midazolam and morphine are summarized (Table 12 for the PST-patients and Table 13 for the PCU-patients).

Ten PST-patients had 12 intractable symptoms while the 16 PCU-patients had 18 refractory symptoms. Physical symptoms (n = 4/10) were substantially present in the PST group (3 pain and 1 dyspnoea and terminal agony) while they represented a minority (n = 2/16) in the PCU-group (1 pain and 1 dyspnoea). In the PST-group existential suffering (n = 4/10) and psychological suffering (n=0/10) were less frequent than in the PCU group (respectively n = 9/16 and 5/16) (Figure 17).

The intractable symptoms came under control within a few minutes for some patients, other patients needed one or more extra midazolam administrations or an increased injection rate to avoid waking up. Forty-eight hours after the start of

sedation, full control of symptoms was reached in 24/26 patients (92%). In one patient of the PST-group (37 year old - female) never came the intractable symptoms (physical pain and anxiety) under control, even with very high doses of morphine and midazolam.

Figure 17: Reasons for palliative sedation in the Palliatieve Support Team(PST) and the Palliative Care Unit (PCU) patients in the University Hospital of Leuven.



The other patient (also of the PST-group; 74 years old female) was started with midazolam IV in a phase of extreme restlessness and terminal agony. She died less than 1 hour after the start of the midazolam. At that moment, already 90 mg of midazolam had been given I.V. without any effect on the symptoms. Midazolam can even have contributed to a hastened death in this patient by causing respiratory depression (a high dose I.V. in less than 1 hour). Thereafter we never have given midazolam I.V. on such a high dose rate and the normal used administration route became as a routine S.C. both for bolus and continuous infusion.

Table 12: Data from all patients who received palliative sedation by the palliative support team(PST) between 1997 and September 1999. Age and gender (female/male), duration of intermittent and/or permanent sedation are shown. The range of doses of midazolam per 12 or 24h .and the parenteral morphine equivalent doses in mg/d. are given.

P.S.T. n = 10	Intermittent Sedation			Permanent Sedation		morphine equiv. dose mg. /d. (S.C/I.V.)
Age F/M	Duration (d.)	midazolam dose mg. /12h.	Commu-nication possible?	Duration (d.)	midazolam Dose mg./24h.	
47 F				5	90	30
68 F				1	15	60
59 F				10	15-45	0
33 F	1	15	Yes	2	30	600
74 F				<1	90	10
37 F	7	90-120	Yes	7	150-450	900-3740
58 F	1	15	Yes	1	60	100
56 F	18	30	Yes	0	0	0
57 F				5	30-75	60-500
35 F				5	15-90	250-2000

Intermittent sedation was done in 9/26 patients for a duration varying from 1 to 33 days with a median of 5 days and a mean of 9 days. These 9 patients were intermittently sedated for a total of 81 days. Three of nine patients asked on the second day to switch to permanent sedation, probably because they felt to be in a too weak general condition at this point, being of no more than 24 – 48 hours

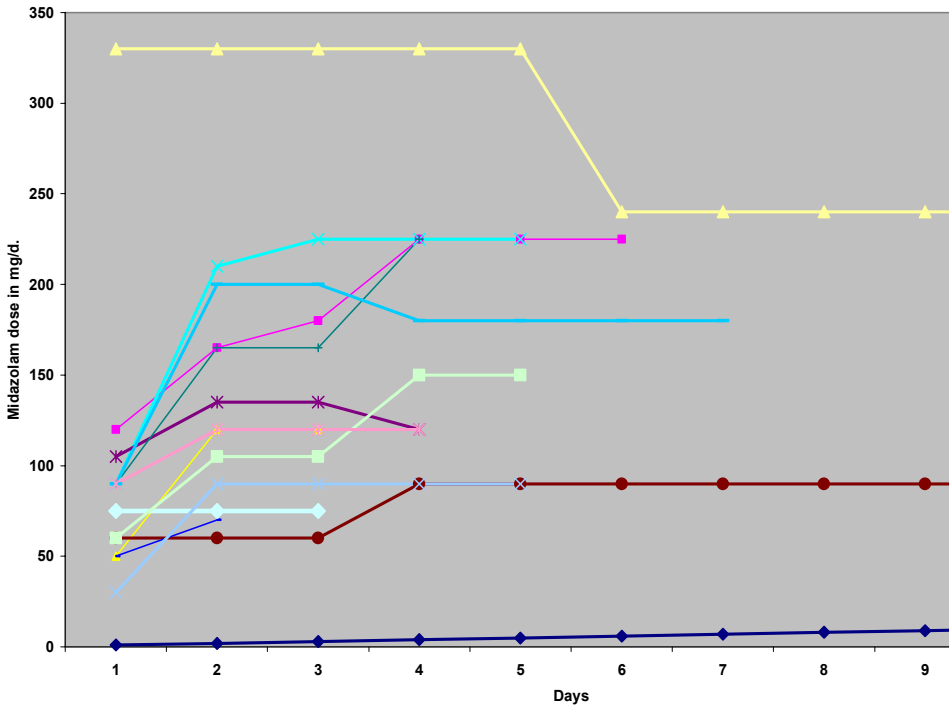
Table 13: Data from all patients who received palliative sedation in the palliative care unit between 1October 1999 and 31 December 2002. Age and gender, duration of intermittent and/or permanent sedation are shown. The range of doses of midazolam and the morphine equivalent dose are given.

P.C.U. N=16	Intermittent Sedation			Permanent Sedation		morphine equivalent. dose mg. /d. (sc/iv)
Age F/M	Duration (d.)	midazolam dose mg. /12h.	Commu-nication possible?	Duration (d)	midazolam dose mg./24h.	
71 F				5	30	30-50
68 M				4	75-90	30
77 F	33	20-90	Yes	10	330	0
71 M	5	30	Yes	5	60-135	60
56 F				2	75	150
60 M				6	75-180	40
47 F				1	30-60	10-20
65 M				3	150-225	300
46 M	1	35	Yes	1	35-60	300
57 F				7	90-225	160
80 M				2	135	0
70 F				4	90-225	500-530
69 M				3	90-120	160
46 F	11	30-45	Yes	1	150	80
73 F	4	30	Yes	0	0	0
59 M				4	120	3000

away from death. This "second line" permanent sedation varied from 1 to 10 days with a mean of 3.85 days and median duration of 2 days. Only 2/9 patients were intermittently sedated until death for respectively 4 and 18 days. Sixteen of the 25 patients asked to start immediately with continuous sedation and this varied from <1 day to 10 days with a mean of 4 days and a median duration of 4 days.

The individually titrated dose of midazolam in the intermittent sedation group varied from 15 to 120 mg/12h while the continuous sedation group was treated with doses midazolam of minimum 15 and maximum 450mg/24h. (Figure 18).

Figure 18: Individual doses midazolam per patient are shown in function of time from the start of the permanent palliative sedation until death for the last 14 patients sedated at the PCU.



Midazolam has to be individually titrated during the first day, thereafter is the dose mostly relative stable. The patient with the highest dose (330 mg/d.) in the 14 permanently sedated patients in Figure 18 was earlier intermittently sedated for 33 days with midazolam doses between 30 to 90 mg/12 h. At the moment of starting with permanent palliative sedation the midazolam dose was increased to 240 mg/d. Above this high dose , she needed regular bolus injections of 15 mg because there were signs that she was waking up several times a day with the risk of presenting again refractory symptoms.

During the palliative sedation, the pain treatment was continued with a wide variation in morphine equivalent parenteral daily dose from 0 to 3740 mg. /24h. All other medication that was not substantially necessary was stopped (cholesterol lowering drugs, benzodiazepines, diuretics, cardiologic drugs, vitamins, antihypertensive drugs,…)

In the registration period of this study 10/750 PST-patients (= 0.13%) and 16/511 PCU- patients (= 3.13 %) were totally sedated for palliative reasons. Between September 1999 until 2002 there was a yearly gradually increasing number of dying patients on the palliative care unit while the absolute number of patients asking for palliative sedation remained stable (Figure 19). The percentage of dying patients that asked for palliative sedation decreased over these 4 years from 7.5 to 2.4% (Figure 20).

Figure 19: Number of sedated palliative patients on the palliative care unit related to the number of admitted and dying patients in the PCU.

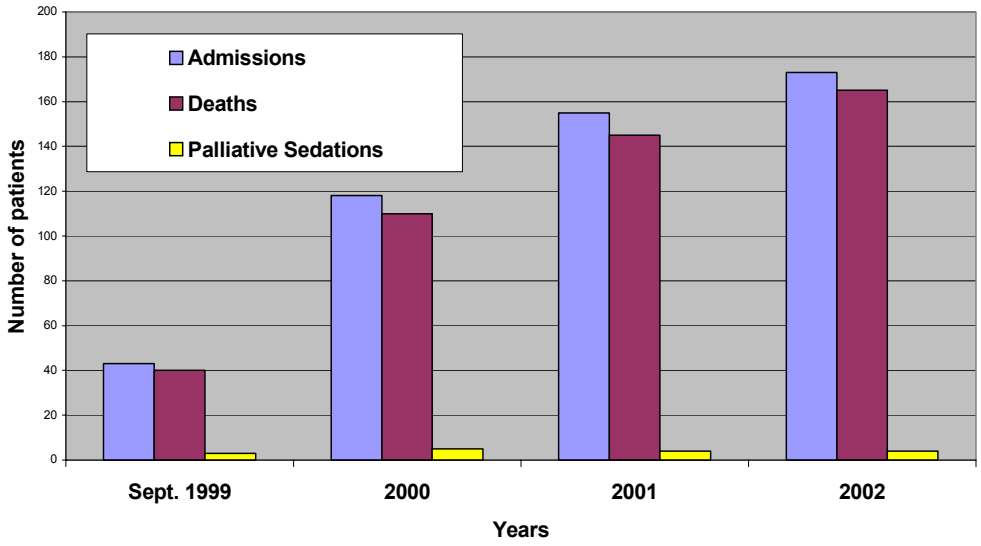
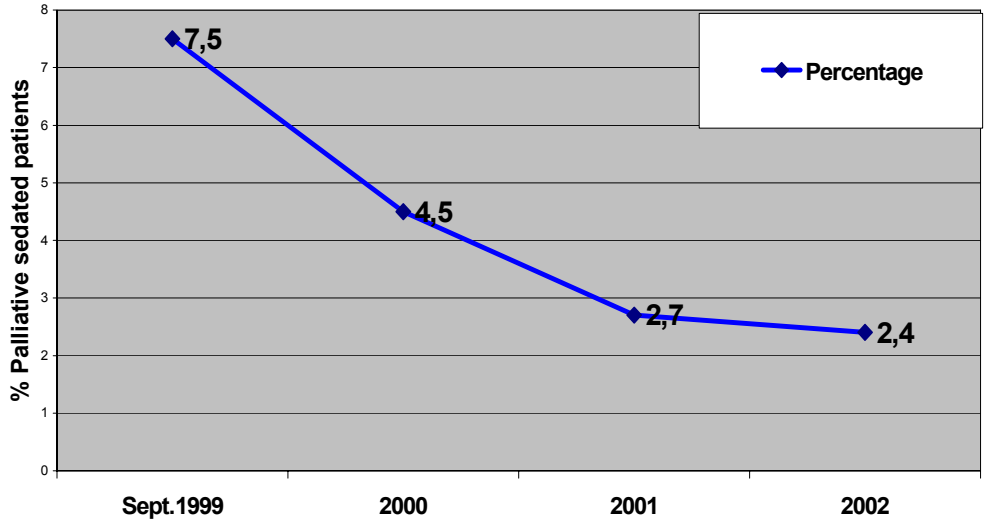


Figure 20: Percentage of terminal palliative patients who asked for palliative sedation to relieve refractory symptoms on the P.C.U. of the U.H. Leuven.



5.4 Discussion

5.4.1 Indications for palliative sedation

There is a shift in the indications for palliative sedation in this study over the 5 years of registration with a decrease of physical intractable symptoms[1] (4/10 =40% to 2/16 =12.5%) but development of more existential and psychological suffering[2] (4/10 = 40% to 14/16=87.5%). The PST-group are patients for whom the treating team can ask for palliative advice from the hospital based palliative support team. The second group is a palliative care unit group of patients that is cared for by palliative professionals on a dedicated palliative care unit with in general more clinical experience in pain- and symptom control. Also the two different treatment era's ('97-'99 and '99-'02) can be responsible for a difference in palliative expertise and attitudes. Existential (n = 13) and psychological suffering (n = 5), anxiety and terminal restlessness (n = 6) combine 72.7% (24/33 symptoms) of the palliative sedation indications in this study. This is in contrast with the data of Fainsinger (99) that in a multicenter study identified mainly physical indications (pain, nausea and vomiting, dyspnoea and delirium) for palliative sedation. Existential 'distress' was only present in 7/397 of his patients (<2%). But more than one-third of his patients were not informed about their diagnosis and the patients stated that they did not wish to have any further information. This reflects cultural differences. In our patients on the PCU the diagnosis is disclosed and the patients know that they are in a PCU where cure is no longer possible; they are admitted just for care and symptom control, to optimize the quality of their ending live. The disclosed truth might have contributed to the feeling of hopelessness for several of these patients.

[1] (3 physical pain + 1 dyspnoe & terminal agony to 1 physical pain + 1 dyspnoe & terminal agony)
[2] (4 existential suffering to 9 existential + 5 psychological suffering)

It's amazing that family distress is an indication for palliative sedation of the patient in the Spanish cohort of Fainsinger's study. Selected palliative care experts use sedation at the end of life for pain (20%), anguish (14%), respiratory distress (12%), agitation, delirium, confusion, hallucinations (12%), fear, panic, anxiety, terror (10%), emotional, psychological, spiritual distress (10%) restlessness (10%) seizures, twitching (4%), nausea, vomiting, retching (2%) and others (6%) (99). There is still some confusion about the indications. Morita describes "terminal sedation for existential distress" in terminally ill cancer patients who expressed existential distress by saying, "their lives were meaningless". Although the title suggests that existential distress is the main indication for sedation, the target symptoms for sedation were dyspnoea (n= 10), agitated delirium (n= 8), pain (n= 1) and psychological distress (n= 1) (97).

In a review 13 published studies on "terminal" sedation have been summarized. The reported indications for terminal sedation were: dyspnoea (11/13), pain (11/13), delirium (9/13), nausea and/or vomiting (7/13), but psychological 'distress' in only 2 studies. (98).
It is clear that variable incidences of refractory symptoms still exist in palliative cancer patients. Does this reflect differences in palliative skills, different measurements, inter-individual variability of assessments or is this influenced by cultural and spiritual factors?

5.4.2 Effectiveness of symptom control

In an international multicenter study Fainsinger reported adequate symptom control for "uncontrolled symptoms" in between 53 and 89% terminal patients (99). We always discuss with our patients and their family the intensity of sedation that will be given. All patients choose to progressively increase the dose of midazolam until unresponsiveness occurs, to really avoid any prolonged suffering. Symptom control was reached in 24/26 patients (=92%) after <48hours

and had to be checked continuously for each individual patient by control of patient's reactions after giving external stimuli. The first day of the sedation is used to optimise the dose of midazolam in function of symptom relief. The patients with intermittent sedation are all able to communicate and to convince us that they are satisfied with the intermittent sedation for 1 or more days.
In only 2 out of 26 patients the intractable symptoms were not controlled. One patient died within one hour after the start of sedation without getting any benefit from the treatment and the second patient her symptoms were really resistant to even very high doses of midazolam (450mg./24h.) and morphine (3740mg./24h.). None of these 2 patients became unconsciousness.

There is some debate in the literature regarding the appropriateness of sedation for refractory symptoms that are psychological as opposed to physical in origin (98). In this study there was no difference in effectiveness since total unconsciousness takes away both physical and psychological symptoms.

5.4.3 The duration and type of palliative sedation

The short period of palliative sedation between 1 to 7 days for 92% (24/26) of patients is consistent with the 1- 6 days in the literature (99). Only 2/26 of our patients were totally and permanently sedated for a maximum of 10 days.

Very few authors mention the possibility of intermittent palliative sedation and nobody discloses some personal experience. Nine patients were intermittently sedated in our hospital during 82/177 (= 46%) sedation days. The patients and their families evaluated these days as useful "life", as valuable time before death. The patient can ask at any moment to switch from intermittent to permanent sedation when the personal perception of quality of life decreases. The 82 "good quality of life" days are net benefit for these patients with otherwise unbearable symptoms and also of some benefit for their families. These days are an

important argument against euthanasia. Intermittent palliative sedation promotes life in this selected group of patients while euthanasia would stop life. This proves that palliative sedation is not slow euthanasia. It realises symptom control, in respect for the wishes and the autonomy of the patient since the patient will choose if he/she prefers intermittent or permanent sedation and he/she has to decide if and when the intermittent sedation has to been changed to permanent sedation.

5.4.4 Frequency of palliative sedation

Palliative sedation is rarely indicated (0.13%) in a hospital population served by a palliative support team, but the indication is more frequently (3.13%) seen in a palliative care unit with more complex clinical and psychological problems and patients who are not (longer) or less supported by a social or family network of palliative care.

The decreasing percentage of palliative sedation in the PCU can be explained by the progressively more skilled and experienced palliative team with consequently fewer refractory symptoms. Secondly, the very transparent interdisciplinary procedure, that was developed to manage the indications for palliative sedation, results in unambiguously clear information to patients and their families by both professional caregivers and volunteers. The well-informed patient develops less terminal anxiety, less distress and is more confident in the dying process while maintaining his/her autonomy. In this situation patients less frequently request palliative sedation. Extrapolation from literature or other clinical practices has to be done with caution because also in palliative sedation there seemingly is a clear learning process to handle new treatments and protocols. There still is, and most likely will remain, a great variation in clinical practice, in skills, knowledge, attitudes, interdisciplinarity, cultural and psychosocial attitudes between services and countries concerning palliative care settings. It is possible that some patients with refractory symptoms maybe will choose for euthanasia above palliative sedation in countries where euthanasia is legalized.

5.4.5 Medications used for palliative sedation

Midazolam is the drug of choice for inducing palliative sedation. In the cited palliative expert study, all respondents from the UK (n=20) and three-quarters of Canadian respondents (n=19) used midazolam as the primary drug to induce sedation (96).
In our study midazolam was the only drug used to sedate with doses varying from 15 to 120 mg/12h. for intermittent palliative sedation and from 15 to 450 mg/24h. for continuous palliative sedation. This wide range of doses proves that a simple kitchen recipe for palliative sedation does not exist but that drug dose has to be adapted to the individual patient's needs.

Although cancer patients seem to develop some tolerance to painkillers over the first 2-4 months, there is no suggestion in figure 18 that there is some tolerance to midazolam during the palliative sedation.

5.4.6 Ethical considerations

Some authors defend the use of palliative sedation at the end of life with the rule of double effect. But the same rule causes reluctance for many physicians to use sufficient doses of opioid analgesics, even when their patients are dying, in part because of fear (both ethical and legal) of contributing to an earlier death (100). The rule of double effect makes it ethically possible to use sufficient doses of morphine to control cancer pain; it can however also be used when pain erroneously is considered as refractory. The rule of double effect fails to take the patient's wishes into account and this makes its use problematic in many circumstances at the end of life (101).

There are 4 key conditions for the rule of double effect:

- The nature of the act must be good
- The good effect must be intended and not the evil effect
- Distinction between means and effect; the bad effect must not be a means to the good effect
- The proportionality between the good and the bad effect: the good effect must outweigh the bad effect.

Thus one should choose the action with the most favourable balance between good and bad effects, within the limits set by the first three conditions. In palliative sedation there is the bad effect of the unconscious state that deprives the patient of further communication. Palliative sedation does not intend and will not result in shortening life when midazolam is given cautiously by an experienced team. These patients will always die within days (about 90% will within a week) due to disease progression. Our multidisciplinary team perceived it as unethical to let patients suffer during their last days of life while they ask for help. This help can be given in a feasible and effective way by intermittent or permanent palliative sedation.

Palliative sedation remains controversial; some view it as “slow euthanasia” (102) because the patient not only is sedated to the point of unconsciousness but will also be deprived of nutrition and fluids (103). An important consideration is that death can never be caused within a few days just by withholding fluid or food. The majority of our patients however had already stopped eating for some days or even weeks before the start of the palliative sedation. Some patients stopped ingestion due to the inability to swallow caused by tumour progression others voluntarily stopped eating to avoid futile life prolongation. Those who did not yet stop eating before palliative sedation ask to be no longer fed during palliative sedation or not to receive treatments that can prolong their life. The opposite question has to be asked: is it ethically justified to try to prolong the life

of these patients by administering fluids and foods, while the patient would suffer without palliative sedation?

Some authors don't see any difference between slow euthanasia and palliative sedation because the result is the same in their mind. Both interventions have the aim to stop suffering and both end by death. Morita showed in a prospective study that there is no statistical difference in survival rate in palliative patients who did or did not receive strong sedatives (104). So there is no justification to believe that midazolam shortens life. Palliative sedation is the ultimate tool to relieve otherwise intractable suffering. This tool can be used worldwide and doesn't need any change of the laws, as is necessary for euthanasia.

Palliative sedation can ethically be justified by the principle of proportionality. Sedation is an exceptional treatment for an otherwise intractable symptom. The only alternative for relief of the suffering of these terminal palliative patients is euthanasia or suicide. In our practice, the treating physicians and all patients, except one, preferred palliative sedation to euthanasia.

Ganzini et al. (105) found that hopelessness but not depression was associated with a willingness to consider assisted suicide in amyotrophic lateral sclerosis patients. For in-patients with psychiatric disorders, hopelessness is a better predictor of suicidal intent and actual suicide than depression (106). The existential and psychological suffering in these palliative patients can be caused by the hopelessness that is experienced by some terminal patients. This study shows that when physical symptoms are better controlled, more existential and psychological issues will arise. This is a new and continuing challenge for caregivers and all palliative teams; they have to be conscious and aware of the changing patterns of symptoms in their patients.

In an era of legalisation of euthanasia in the Netherlands and Belgium, some patients, family members and some caregivers view euthanasia as a right that can

be obtained on demand. It recently became by law one of the options that can be freely considered by terminally ill patients with extreme suffering. Physicians and palliative caregivers should not encourage patients to hasten death, even when practising in a jurisdiction that allows euthanasia or assisted dying. They should clarify the request, explore and address the patient's concern, achieve a shared understanding of the goals of treatment, search for less harmful alternatives, express to the patient what they are willing to do, discuss the relevant legal issues, and share their decision-making with competent colleagues (107). It is important to remember that physical and mental suffering justifies euthanasia in the Netherlands but the public prosecutor recently established jurisprudence. A general practitioner was guilty of helping an 86-year old man with no serious physical or mental illness to commit suicide for "existential pain" or "being tired of life ". Existential pain is not a justification for euthanasia or physician assisted suicide.

5.5 Conclusion

Palliative sedation can be a valuable alternative to euthanasia or physician assisted suicide for many terminal patients with intractable symptoms. It is an effective (92%) but exceptional (about 0.13% in the hospital and about 3% of all dying persons in the palliative care unit) treatment for the rare intractable symptoms at the end of life.

Most authors reported about refractory physical symptoms as indications for palliative sedation but this study shows a shift to more existential and psychological indications over the years. The practical implementation of palliative sedation for the individual patient can only be formulated following an interdisciplinary consultation with respect for the wishes and the autonomy of the patient and his family.

Intermittent sedation was able "to add life to the days but does not add days to life" in the ending lifetime of patients who choose for this type of sedation. In

deeply sedated patients there is no shortening of life compared to less deeply sedated patients, according to the literature. It is obvious that disease progression causes death or that the withholding or the withdrawal of food and fluids (mostly already chosen by the patient some days or even weeks before the start of the palliative sedation) will stop prolonging the dying process. Sedation has to be based on individual drug titration; a simple recipe to define the necessary drug dose does not exist.

Palliative sedation is necessary for only a short time (1 to 10 days) before death and is ethically justified because the sedation constitutes a balanced response to the otherwise unbearable symptoms.

Chapter VI

Conclusions and perspectives

6.1 Emergency hospital admission for pain in palliative cancer patients

Pain is a frequent symptom during the home care of advanced cancer patients and is in this study responsible for 59% of emergency hospitalizations of palliative oncological patients. In the hospital, etiological and symptomatic oncological treatment was started for 54% of the patients. This sounds amazing for many caregivers since these advanced cancer patients had already stopped anti-tumor treatment. Any new serious symptom however needs an open minded approach by the appropriate disciplines to balance the advantages and disadvantages of possible treatment modalities. When possible a therapy eliminating the cause of the pain is the most effective one. In the mean time, an immediate analgesic therapy is required to realize symptom relief. When etiological pain treatment is no longer feasible, symptomatic treatment is obligatory. Medical decision making in cancer patients is a dynamic process until death, since individual disease progression and complications usually are unpredictable. This holistic approach requires concertation between different disciplines that work interactively and in close contact with home caregivers. This is the best guarantee that the patient can be appropriately discharged as soon as possible to a home care setting. All persons involved have to fulfill the wish of palliative patients to return home. Caregivers at home are skilled and experienced in the palliative home care possibilities to enable continuity of the hospital initiated care.

In a prospective registration study over 3 months, patients admitted in emergency in the department of oncology with pain as sole complaint or one of the complaints were rapidly diagnosed, started with therapies that were individually tailored and were cared for when necessary until death. This implies that all aspects of oncological and palliative therapeutic skills are available as well as a palliative care culture. Physicians have to realize that their role progressively decreases but never will stop during the patient's life. During the course of the disease a close cooperation with nurses, social workers, dedicated psycho-oncologists and spiritual

caregivers gradually develops. Awareness of the progressively changing role of caregivers at the end of life is of paramount importance.

Integration of home and hospital care remains a major challenge. This study provides evidence for the complementary role that hospital wards can have for the many home cared palliative cancer patients who suffer from pain. The study suggests that home caregivers and patients have realistic expectations. Patients were not dropped off at the emergency department, but were referred mostly with a letter formulating the questions or expectations for the future. Few patients entered during the weekend but most waited to get advice by their general practitioner on Monday. This highlights the important function of the general practitioner as "health care manager" for palliative cancer patients. These emergency situations almost never are immediately life threatening, but ask for a quick and effective solution. Most patients probably did not need emergency hospital admission but could also have been helped by an at short notice (within 48 h.) planned hospitalization. Therefore a prior consultation and admission planning policy between general practitioner and hospital based physician is preferable, to limit emergency hospitalization to those patients who really need this and to avoid the burden of emergency admission for all parties involved. General practitioners need to have an easy contact with the hospital caregivers, by phone or e-mail, for advice and planning. Specialists need a facility to admit patients rapidly for observation and treatment.

6.2 Strong opioid use on a long term basis in elderly cancer patients

In all palliative care settings pain still is too much present. Since a few decades international experts have established validated guidelines stating, that the use of strong opioids by mouth, by the three steps W.H.O. ladder and by the clock, is the key solution to relief pain for many cancer patients. Morphine myths still survive in the mind of many caregivers and patients, frequently precluding an adequate pain

therapy because many people try to postpone or even try to avoid the use of strong opioids. There is some restraint, especially for elderly people, to start strong opioids because of fear of addiction, of development of tolerance, of somnolence, of confusion and of respiratory depression. These myths can only be refuted by solid clinical research data. Therefore the use of TTS-fentanyl was studied in 341 patients over 60 years belonging to a group of 661 TTS-fentanyl treated patients. There was effective pain control and the development of opioid tolerance was similar for elderly as for all patients. Elderly patients had slightly more constipation but there was no increased use of laxatives in the elderly; all the other side effects were comparable with those of the other patients. Confusion in the elderly is feared, but was only present in less than 5%.

The appreciation and convenience of the TTS-fentanyl patch were good to excellent also for the patients above 60 years. The secret for this good tolerability is that the opioids were given in individually tailored doses according to the international guidelines. Side effects are slightly more frequently seen, especially in the frail elderly persons, when the morphine dose is increased too rapidly or not increased adjusted according to pain intensity. The aged persons (>70years) used somewhat less TTS-fentanyl, maybe because these patients did not report their pain intensity as effectively as the younger persons did or because caregivers were hesitating to increase the opioid dose. These study results suggest that all ages of patients can tolerate an effective pain treatment with strong opioids. Age no longer is a reason to exclude patients from pain treatment.

We strongly advocate that knowledge, skills and attitudes of effective cancer pain relief are part of the basic education of both physicians and nurses. It's the aim that all physicians and nurses can handle cancer pain more effectively in the near future just by implementing the now available knowledge and using the existing guidelines; they really need guidelines for the daily clinical use of pain measurement tools, pain control standards and follow up procedures. Pain

management has to be an institutional priority and research has to be done also in terminal cancer patients to develop more appropriate clinical guidelines.

6.3 Opioid tolerance: a self-limiting phenomenon

Many patients, families, nurses and physicians postpone effective pain treatment with opioids to the final part of the end of life, "to reserve this effective pain treatment for the difficult terminal phase of life". They fear to be powerless against the problems of pain and symptom control in the dying process, if opioid tolerance indeed would develop. Many expert palliative authors and pain specialists have declared that tolerance is not that important and that opioid tolerance cannot justify withholding effective pain relief in suffering patients. In the meantime many patients suffer worldwide from cancer pain that easily could be treated. Scientific data that invalidate the clinical importance of opioid tolerance are lacking.

For the analysis in chapter IV we selected the long (>13 weeks) surviving advanced cancer patients who used TTS-fentanyl as maintenance treatment and an 'as needed' dose of morphine as rescue medication for incidental or breakthrough pain. By selecting long-term survivors the effect of tumor growth on opioid consumption is minimized, allowing to estimate the development of opioid tolerance. The sometimes enhanced analgesic consumption pre-mortem cannot be distinguished from opioid tolerance in this study. Our data do not indicate the development of opioid tolerance after 4 months until 2-years of follow-up. During the first 4 months the mean opioid dose progressively increases over time and this probably reflects real opioid tolerance. The results of this study offer scientific evidence that some opioid tolerance develops during the first 4 months. This is a clinically negligible long-term issue in cancer pain treatment. Opioid tolerance does not induce an exponential long-term increase of the opioid dose and yet an acceptable level of pain relief is maintained. Tolerance development seems to be limited both in quantity (increase of the daily opioid dose to about 150 µg/h TTS-fentanyl) and in time (3-4 months).

The required doses increase progressively during the 4 first months; these data seem valid because of the large number of patients. The other end of the curve is less sure because the deaths are spread over 21 months. It could be interesting to study the fentanyl consumption during the last few months of life, as consumption may be less stable at that time. Having eliminated both the first non-stable part of 4 months and the pre-mortem non-stable part when present, the middle part can definitely answer to what extent tolerance increases beyond 4 months, excluding the issues of fast tumor growth or the dying process. It would be very interesting if this analysis could be done in the future. Further would it be valuable if somebody else could confirm these data concerning the opioid tolerance in cancer pain management.

6.4 Indications for palliative sedation

There is overwhelming evidence in the literature that the existing knowledge of pain pathophysiology and the different analgesics used according to the existing WHO guidelines can relieve more than 90% of the cancer pain, bringing the VAS pain score below 3.5. Occasionally, cancer pain is refractory to analgesic therapies. For already 6 years we have used the option of palliative sedation for these patients. This was only done at the explicit request of the suffering, well-informed and conscious palliative terminal patient. A shift in the indications for palliative sedation is seen over 6 years of registration; physical intractable symptoms are decreasing (4/10 = 40% (PST) to 2/16 = 12.5% (PCU)) and existential or psychological refractory suffering is increasing as indication (4/10 = 40% (PST) to 14/16 = 87.5% (PCU)). The PST-group are ward patients for whom the treating team was advised by the palliative support team, while the palliative care unit patients (PCU) are cared for by palliative professionals more experienced in pain and symptom control. The two different treatment era's '97-'99 (PST) and '99-'02 (PCU) may reflect an evolution in palliative knowledge and attitudes. Existential and psychological suffering, anxiety and terminal distress constitute 72.7% of the indications for palliative sedation in this study. Does this mean that the truth is

unbearable for some patients and that the disclosure of the diagnosis and prognosis creates existential suffering? We may also suggest that physical pain currently is the best amenable symptom in cancer patients; if this symptom is relieved, the patient starts reflecting on the story of his life and can end up with anxiety, distress, depression and/or existential suffering. All these symptoms are less amenable to treatment than physical pain. Even with more social workers, more psychologists and more chaplains, some amount of intractable non-physical suffering will always be left. It will be more difficult to make the same progress in the treatment of non-physical suffering as there was in physical pain. Some persons in the Netherlands and Belgium think that this problem can be solved by the principle of absolute autonomy and an euthanasia law. In the Netherlands, in Oregon (US) and parts of Australia physician assisted suicide has become legalized. Will this be the way to solve the problems in the near future? Do we have to provide such escape routes for patients with intractable symptoms?

Or should we return to the first principles of palliative care when 'love and tender care' were the strongest weapons in an era that physical pain was not so treatable as nowadays? In our opinion, one should combine this soft option with correct scientific physical care, implementing the efficacy of modern medicine, with adequate communication and interaction focusing on both the patient and the family. With this holistic approach to the palliative patient, combined with a growing palliative experience, the frequency of refractory suffering or hopelessness asking for palliative sedation, decreased from 7.5 to 2.4 % in our palliative care unit over 4 years. The dying process is dignified by focusing attention on the patient and his family, by listening to them, allowing them to fulfill "their good death" while the caregivers are witnesses, ready to help and to correct where necessary.

Healthy caregivers and politicians do not have the right to judge patients' dignity (108). Studies show that 93% of patients selves in palliative care units did not report significant loss of dignity. Only 7% reported moderate or severe loss of dignity.

Death and dying are not inherently undignified for patients, as sometimes perceived by healthy persons. There is a danger that loss of dignity may be overstated, extrapolated from a few unrepresentative cases that should have become obsolete. Research shows that not pain but depression is associated with a desire for euthanasia or physician-assisted suicide (109). These results illustrate that common perceptions about the dying process are often wrong and misguided. These misperceptions probably arise because good deaths do not raise attention, while a few tragic cases reinforce natural fears about dying (108).

Instead of offering death by euthanasia as promoted by some, we have offered some intractable patients life to the days by using intermittent sedation; the other patients were effectively symptom controlled by continuous sedation and were given the opportunity to die symptom free, surrounded by their family. Two patients, in the early less experienced years, were not relieved from their symptoms by palliative sedation.

It is our conviction that palliative sedation is in the majority of the patients by far preferable to euthanasia, since the main goal, a dignified and pain free death, the best option for both patient and families, is reached in a more satisfying and natural way. Research of the dying process, to understand what really matters for the patients and how they would like to be cared for, remains a major clinical challenge for the next years.

Summary

Cancer is responsible for 25% of all deaths in the Western world. About 80% of all terminal cancer patients suffer from suboptimal pain treatment. However, cancer pain can be relieved in more than 80% of the patients. Caregivers have to implement the existing knowledge of pain pathophysiology and to follow the internationally validated pain treatment guidelines with an individually tailored selection of the available analgesics. In the present thesis, 4 questions of effective cancer pain treatment in daily clinical practice have been investigated.

Cancer pain is an important human and social issue that was either the only or one of the most important symptoms leading to emergency hospitalization in the Leuven oncology department for 59% of advanced palliative cancer patients (Chapter II). Oncologists made rapid diagnoses, starting individually tailored therapies and cared for some patients until death. Such holistic approach requires a judicious balancing between all aspects of oncological and palliative therapeutic skills, as well as a palliative care culture. Medical decision making remains a dynamic process in advanced palliative cancer patients, involving more and more different disciplines as new clinical and practical problems develop towards the end of life. Awareness of the changing role of different caregivers at this phase of the patient's life is important. A close cooperation between the different hospital based disciplines, in close contact with the home caregivers, is the key issue to relieve the total pain of the individual patient.

Treatment is more and more limited to pain and symptom control when oncological treatments no longer are useful. There is still some reluctance to treat cancer pain with heavy medication over long periods of time, especially in the elderly patients. Analysis of the strong opioid use in a large group of elderly patients (chapter III) confirms that age does not substantially influence the profile of adverse and side effects during long-term use of strong opioids. Constipation was slightly more

frequent in elderly patients while the incidence of the other adverse effects was equal to that of the total group. These results provide evidence that all patients can tolerate an effective pain treatment with strong opioids even for long periods of time. Age is no longer a reason to exclude terminal patients from effective cancer pain treatment.

The myth of development of tolerance to strong opioids already persists for several decades while valid scientific data to substantiate this myth in clinical practice are lacking. The results of chapter IV in this thesis scientifically validate the clinical experience that the development of tolerance to strong opioids is limited both in quantity and in time. Opioid tolerance does not induce an exponential long-term increase of the opioid dose needed. The phenomenon of a possible drug tolerance development was observed during the first 4 months of treatment. After this initial time, a relatively stable opioid dose realized an effective pain control until death for most patients. Further research on the chronic consumption of strong opioids by cancer patients has to be encouraged.

Cancer pain however cannot always be totally relieved by strong analgesics. All aspects of the "total pain" concept can become refractory to standard treatment; this is rarely physical pain, but in 75% of the patients this is psychological or spiritual suffering, less frequently social suffering. For many of these patients palliative sedation was an ultimate but highly effective tool to relieve these "intractable symptoms" in our hospital. The difference between "to let die", while maintaining symptom control by palliative sedation, and "to hasten death or to shorten life" by euthanasia is highlighted. Ethical considerations are given on this highly controversial subject.

A comprehensive approach to cancer pain relief asks for interdisciplinary cooperation of skilled medical and paramedical professionals. It remains a challenge to develop better cancer pain relief and control of other palliative

symptoms. The understanding what really matters for patients, how they would like to be cared for and the optimalization of the process of dying are other challenges for the next few years. Scientifically derived data will have to provide the basis for further improving pain and symptom control.

Samenvatting

Kanker is in de Westerse wereld verantwoordelijk voor 25% van alle doodsoorzaken. Ongeveer 80% van alle terminale kankerpatiënten lijden pijn door onvoldoende behandeling. Deze pijn kan echter behandeld worden in ruim 80% van de patiënten. Hulpverleners moeten de bestaande kennis van pijnpathophysiologie toepassen in de praktijk. Ze zouden ook de internationaal erkende pijnbeleidslijnen moeten gebruiken om tussen de beschikbare pijnstillers te komen tot een geïndividualiseerde aanpak. In dit proefschrift worden een viertal aspecten van effectieve pijnbehandeling in de dagelijkse praktijk onderzocht.

Kankerpijn is een belangrijk menselijk en maatschappelijk probleem. Alléén of als één van de meest belangrijke symptomen, is ze oorzaak van opname bij 59% van de uitbehandelde kanker patiënten die in urgentie op de oncologie afdeling van de Universitaire Ziekenhuizen te Leuven worden opgenomen (Hoofdstuk II). De oncologen stellen op korte termijn diagnoses, starten individueel gerichte oncologische behandeling en verzorgen sommige patiënten tot aan de dood. Deze globale benadering vereist een juiste balans tussen oncologische en palliatief therapeutische deskundigheid, maar vraagt ook een palliatieve zorgcultuur. De medische besluitvorming blijft bij de uitbehandelde palliatieve kankerpatiënt een dynamisch proces, waar meer en meer disciplines betrokken worden naarmate nieuwe klinische en praktische problemen ontstaan bij het einde van het leven. De respectievelijke hulpverleners moeten zich bewust zijn van hun veranderende verantwoordelijkheden in deze levensfase van de patiënt. Echte interdisciplinaire samenwerking tussen al de ziekenhuishulpverleners, in nauwe samenwerking met de thuiszorg, is de sleutel om een goede pijnverlichting te bereiken voor de individuele patiënt.

De behandeling zal progressief zich meer en meer beperken tot pijn- en symptoomcontrole, wanneer oncologische behandeling niet langer meer aangewezen is. Er is enige terughoudendheid om kankerpijn voldoende assertief te behandelen over langere periodes, vooral bij de oudere patiënten. De analyse van het gebruik van sterke opioiden in een grote groep oudere patiënten (hoofdstuk III) bevestigt, dat leeftijd de tolerantie of het nevenwerkingprofiel tijdens langdurig gebruik van sterke opioiden niet beïnvloedt. Oudere patiënten blijken meer frequent geconstipeerd te zijn ten opzichte van de totale groep. Deze resultaten tonen aan, dat alle patiënten een efficiënte pijnbehandeling met sterke opioiden kunnen verdragen, ook over langere tijdsperiodes. De leeftijd kan dus niet meer langer een reden zijn om terminale patiënten efficiënte pijnbehandeling te onthouden.

De mythe van het ontwikkelen van gewenning aan sterke opioiden houdt al verschillende tientallen jaren stand, hoewel goede wetenschappelijke gegevens hieromtrent in de kliniek ontbreken. De resultaten in hoofdstuk IV in deze thesis onderbouwen wetenschappelijk de klinische ervaring dat het ontstaan van gewenning aan opioiden zowel kwantitatief als in de tijd een beperkt fenomeen is. De gewenning aan opioiden doet over langere tijd geen exponentiële stijging in dosis ontstaan. Een mogelijke opioidgewenning werd enkel gezien in de eerste 4 maanden van de behandeling. Na deze aanvangsperiode, kon een verdere stabiele dosis opioiden bij de meeste patiënten de pijn controleren tot aan de dood. Verder klinisch onderzoek betreffende het chronische gebruik van sterke opiaten bij kankerpatiënten moet aangemoedigd worden.

Kankerpijn kan echter niet altijd even effectief behandeld worden met sterke opioiden. Alle aspecten van “totale pijn” kunnen weerstandig worden aan de standaardbehandelingen. Soms is dit lichamelijk lijden, maar in 75% van de patiënten is dit psychisch of spiritueel lijden, zeldzamer sociaal lijden. Voor veel van deze patiënten was palliatieve sedatie in ons ziekenhuis het ultieme maar zeer efficiënte middel om deze “onbehandelbare symptomen” te controleren. Het

onderscheid tussen “laten sterven”, terwijl palliatieve sedatie de symptomen controleert, en “de dood bespoedigen of het leven verkorten” met euthanasie wordt toegelicht. Ethische beschouwingen worden gegeven over dit hoogst controversieel onderwerp.

Een allesomvattende benadering om kankerpijn te verlichten vraagt interdisciplinaire samenwerking van vakbekwame medici en paramedici. Het blijft een uitdaging om betere controle te krijgen over kankerpijn en andere palliatieve symptomen. Leren begrijpen wat de patiënten echt bezig houdt, hoe ze willen verzorgd worden en betere begeleiding van het stervensproces zijn andere uitdagingen voor de komende jaren. Wetenschappelijke gegevens moeten de basis leveren voor verdere verbetering van pijn- en symptoomcontrole.

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